FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF SITAGLIPTIN PHOSPHATE BY SOLVENT CASTING METHOD

A Dissertation submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfillment of the requirements for the award of the Degree of
MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
SHOBANA.M
REGISTRATION No. 261611002

Under the guidance of
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OCTOBER 2018

Certificate

CHERRAAN'S COLLEGE OF PHARMACY

(Affiliated to the Tamilnadu Dr.M.G.R medical university, Chennai)

Approved by The Govt. of Tamilnadu, Chennai
All India Council for Technical Education, New Delhi
Recognized by pharmacy council of India, New Delhi

CERTIFICATE

This is to certify that the Dissertation entitled "**FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF SITAGLIPTIN PHOSPHATE BY SOLVENT CASTING METHOD"** submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **M.SHOBANA Reg No: 261611002** carried out in the department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore for the partial fulfillment for the degree of Master of Pharmacy under my guidance during the academic year 2016-2018.

This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

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Internal Examiner **External Examiner**

Declaration

DECLARATION

The research work embodied in this work **"FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF SITAGLIPTIN PHOSPHATE BY SOLVENT CASTING METHOD"** was carried out by me in the department of Pharmaceutics, Cherraan's college of Pharmacy, Coimbatore under the direct supervision of **Mr.R.Parthibarajan, M.Pharm.,** Professor Department of Pharmaceutics Cherraan's College of Pharmacy, Coimbatore-39.

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Acknowledgement

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ACKNOWLEDGEMENT

I submit my sincere thanks to our Chairman **Mr. K .C. PALANISAMY** chairman, Cherraan's foundation trust, for providing all the facilities to carry out this thesis work.

My sincere gratitude to my beloved Principal, **Dr.P.Selvam M.Pharm, Ph.D, FNABS, FISNS,** Department of Pharmaceutical chemistry Cherraan's College of pharmacy for his kindly support for my project work and for his encouragement and also providing all facilities in this institute to the fullest possible extent enabling me to complete this work.

With the immense pleasure and pride, I would to take opportunity in expressing my deep sense of gratitude to my beloved guide, **Mr.R.PARTHIBARAJAN, M.Pharm.,** Professor & Department of Pharmaceutics Cherraan's college of pharmacy under whose active guidance, innovate ideas, constant inspiration and encouragement of the work entitle **"FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF SITAGLIPTIN PHOSPHATE BY SOLVENT CASTING METHOD "** has been carried out.

I convey my gratitute to **Mr.J.Karthikeyan, M.Pharm**, Professor, Department of Pharmaceutics for his support and valuable advice for my project work.

It is my pleasure to express my honourable thanks to **Mrs.Rubina Reichal, M.Pharm**,**(Ph.D).,** Associate Professor, Department of Pharmaceutics for sharing her valuable knowledge.

I express my sincere thanks to **Mrs.M.Sangeetha, M.Pharm.,** Department of Pharmaceutical chemistry cherraan's college of pharmacy for her support for my project work.

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I convey my gratitude to, **Karunya University,**

I duly bound to all our **teaching**, **non-teaching staffs, librarians and lab assistants** of Cherraan's college of pharmacy for their valuable help and co-operation.

I am giving greatful thanks to all my **friends** for their help during my project.

I express my heartful gratitude to the **Almighty**, for giving me the right way to achieve the good for my project.

Last but not least, a great thank's from my heart to my beloved **Family members**. They are **my living God**, as who guided me in the rightful way to achieve all my activities. They gave me the incredible effort to become a successful person for bright future in this world. Thank's a lot.

M.SHOBANA

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ABBREVIATION

SYMBOL	ABBREVIATION
Gm	Gram
W/W	Weight/weight
Min	Minutes
µg	Microgram
MI	Milli litre
Nm	Nano meter
°C	Degree centigrade
UV	Ultra violet
Cm	Centi meter
SEM	Scanning electron microscope
RPM	Rotations per minute
OTFs	Oral thin films
FT-IR	Fourier transmitted infra-red spectroscopy
HPMC	Hydroxyl propyl methyl cellulose
KBR	Potassium bromide
DSC	Differential scanning calorimeter
HCL	Hydrochloric acid
PEG	Poly ethylene glycol
FDFs	Fast dissolving films

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Introduction

1 INTRODUCTION[1]

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating, and computer assisted three dimensional printing (3DP) tablet manufacture have also recently become available.

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. The novel technology of fast dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar.

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of the water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all the age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. Dysphagia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck thyroid therapy, and other neurological disorders, including cerebral palsy. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablet was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.

1.1 Salient feature of fast dissolving drug delivery system

1. Ease of administration for patients who are mentally ill disabled and

uncooperative.

2. Require no water.
3. Overcomes unacceptable taste of the drugs.
4. Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Cost effective.

1.1.1Need for fast dissolving drug delivery systems

Fast dissolving drug delivery systems can improve acceptance and compliance in patients with dysphasia. Similarly, from market point of view, introduction of FDDS will assist life cycle management of drug especially if the drug is patent protected.

1.1.2 Dysphasia

Dysphasia, or difficulty in swallowing, is common all age groups. According to a study dysphasia is common in about 35% of the general population, as well as an additional 30-40% elderly and 18-20% of all persons in long term care facilities. Common complaints about the difficulty in swallowing tablet due to size, surface, form and taste of tablets. Geriatric and pediatric patients and travelling patients who may not have ready access to water are in the need of easy swallowing of dosage forms. These studies show an urgent need for a dosage form like FDDS that make tablets disintegrate in the mouth without chewing or additional water intake and thus improve patient compliance.

1.1.3 Market view

The need for noninvasive delivery systems continues due to poor patient compliance with existing delivery regimens, limited market size for drug companies and drug uses, coupled with high costs of disease management. Pharmaceutical marketing is one reason for the increase in available fast-

dissolving/disintegrating products. As a drug entity reaches the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A dosage form allows the manufacturer to extend the market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast dissolving/disintegrating formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient population.

1.1.4 Advantages

These rapid dissolving films offer several advantages like,

1. Due to the presence of large surface area, films provide rapid disintegrating and dissolution in the oral cavity.
2. Convenient dosing.
3. Fast disintegration or dissolution followed by quick effect which is desirable in some cases such as pain.
4. Oral dissolving films can be administered without water, anywhere, anytime.
5. Suitability for geriatric and pediatric patients, who experience difficulties in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans.
6. No risk of choking.
7. Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling, storage and enhanced stability.
8. Beneficial in cases such as motion sickness, acute pain, allergic attack or coughing, where an ultra rapid onset of action required.
9. As compared liquid formulations, precision in the administered dose is

ensured from each strip of the film.

10. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
11. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
12. Improved patient compliance.
13. Life cycle management.
14. Difficulties caused from swallowing tablets are circumvented, that is especially advantageous for pediatric and geriatric patients are in diseases with nausea or vomiting.

1.2 FAST DISSOLVING FILMS[2]

Oral films are the newer technologies in the manufacturing of oral disintegrating dosage forms. They are thin elegant films of edible water soluble polymers of various sizes and shapes like square, rectangle or disc. The stripes may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for the water. Fast disintegrating films (FDF s) have a large specific surface area for disintegration. The films alleviate the danger/fear of chocking, easy to handle and administer, maintain a simple and conventional packing that is east to manufacture thus overcoming the short fails of oral fast disintegrating tablets. A major limitation of these dosage forms is low drug loading capacity and limited taste masking options.

Fast disintegrating film is a thin film of 1-10 mm thickness, with area of 1-20 cm^2 of any geometry. Drugs can be incorporated upto a single dose of about 15 mg. The immediate dissolution in saliva is due to special matrix made from water soluble polymers it has usually low tack for easy of handling and

application. However, on wetting the wet tack and muco adhesiveness properties of the system are designed to secure the film the site of application. Flexibility and strength of films are selected to facilitate manufacturing process and process like rewinding, die cutting and packing.

Fast disintegrating film is placed on the patient tongue are mucosal tissue, which gets instantly wetted by saliva. The film hydrates rapidly and adheres onto the site of application. It then rapidly disintegrates and dissolves to release drug for oral mucosal absorption, or for gastric absorption on swallowing.

Table 1: comparison between oral fast dissolving films and oral disintegrating tablets

Oral dissolving films	**Oral disintegrating tablets**
It is a film	It is a tablet
Greater dissolution due to large surface area	Lesser dissolution due to less surface area
Better durable than oral disintegrating tablets	Less durable as compared with oral films
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of chocking	It has a fear of chocking

1.3 FORMULATION CONSIDERATION[3]

Active pharmaceutical ingredient

Film forming polymer

Plasticizer

Sweetening agent

Saliva stimulating agent

Flavoring agent

Coloring agent

1.3.1 Active pharmaceutical ingredient

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the

best candidates to be incorporated in OFDFs. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDF. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation.

1.3.2 Film forming polymers

The primary use of all thin film oral dosage forms relives on the disintegration in the saliva of the oral cavity, the final film that is used must necessarily be water soluble. In order to prepare a thin film formulation that is water soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. It should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. It should not be very expensive and readily available. Microcrystalline cellulose was also used to decrease the disintegration time and improve the dissolution of the drug from the films. Examples of polymers are

- Guar gum
- Xanthum gum
- Acacia
- Tragacanth
- Polyethylene oxide
- Sodium carboxy methyl cellulose
- Hydroxyl propyl methyl cellulose
- Polyvinyl alcohol

1.3.3 Plasticizer

Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. The selection of plasticizer will depend upon its compatibility with

the polymer and also the type of solvent employed in the casting film. Examples of plasticizers are

- Glycerol
- Propylene glycol
- Polyethylene glycol
- Dimethyl phthalate
- Diethyl phthalate
- Dibutyl phthalate
- Triacetin
- Castor oil

1.3.4 Sweetening agents

Sweeteners have become the important part of the formulation intented to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3-6% w/w. both natural and artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as such as sorbitol, manitol, and isomalt can be used in combination as they additionally provide good mouth feel and cooling sensation. However it should be noted that they use of natural sugars in such preparation need to be restricted in people who all are on diet or in the case of diabetic patents. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. The first generation of the artificial sweeteners are

- Saccharin
- Cyclamate
- Aspartame

1.3.5 Saliva stimulating agents

The purpose of using the saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving stripes formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Examples are

- Citric acid
- Malic acid
- Lactic acid
- Ascorbic acid
- Tartaric acid

These agents are used along are in combination between 2-6 % w/w of the stripes.

1.3.6 Flavoring agents

Preferably upto 10 % w/w flavors are added in the OFDF formulations. The acceptance of oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The geriatric population like mint or orange flavors like fruit punch, raspberry etc. it can be selected from synthetic flavor oils, oleoresins peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are the examples of flavor oils while vanilla, cocoa, coffee, chocolate, and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.

1.3.7 Coloring agents

FD&C approved coloring agents are used (not exceeding con centration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. Eg titanium dioxide.

1.4 PROPERTIES OF THE ORAL FILMS[4]

Table 2: Properties of the oral films

PROPERTY	**FLASH RELEASE**	**MUCOADHESIVE MELT RELEASE**	**MUCOADHESIVE SUSTAINED RELEASE**
Area (cm^2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure	Film single layer	Single or multilayer system	Multilayer system
Excipients	Soluble, highly hydrophilic polymer	Soluble, hydrophilic polymer	Low/non soluble polymer
Drug phase	Solid solution	Solid solution/suspends drug particle	Suspension or solid solution
Application	Tongue (upper plate)	Gingival or buccal region	Gingival (or other region of oral cavity)
Dissolution	Maximum sixty second	Disintegration in few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

1.5 OVERVIEW OF ORAL MUCOSA[5]

The oral mucosa is composed of an outer layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelium is similar to stratifies squamous epethelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.

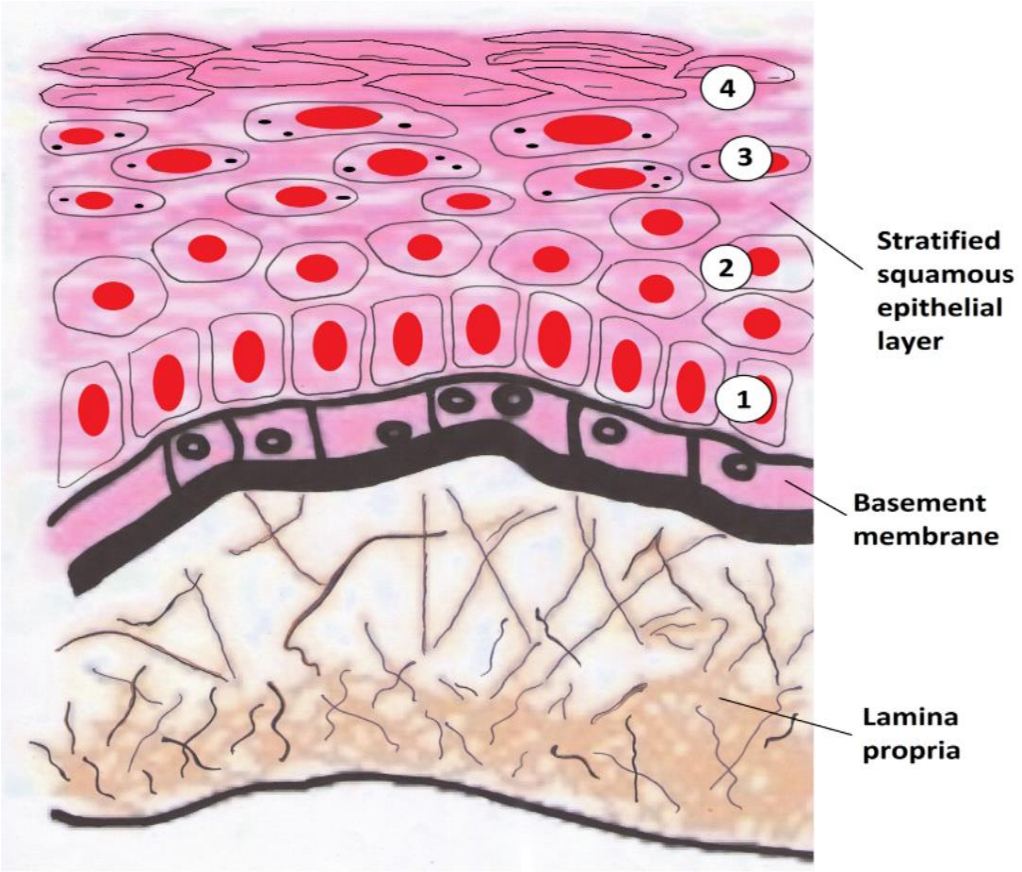

Fig 1: Various layers of oral mucosa

1.6 METHODS OF PREPARATION OF FAST DISSOLING FILMS[6]

One or combination of the following process can be used to manufacture the mouth dissolving films.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

1.6.1 Solvent Casting Method

In solvent casting method water soluble are dissolved in water and the drug along with other. Excipients are dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted into the petri plate and dried.

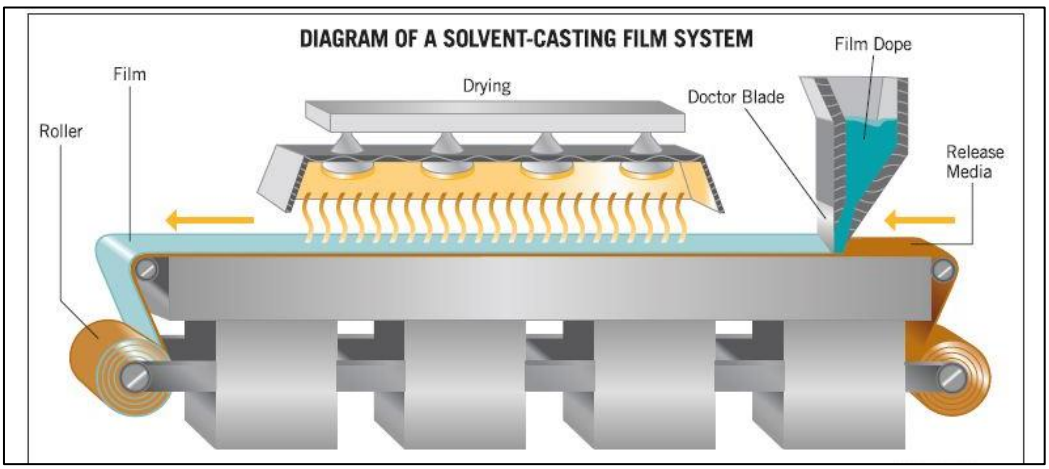

Fig 2: Diagram of solvent casting film system

1.6.2 Semisolid casting

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of

plasticizer is added so toast a gel mass is obtained. Finally the gel mass is casted into the films or ribbons using heat controlled drums. The thickness of the film is about 0.15-0.5 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Both mixtures are mixed to form homogenous viscous solution degassed under vaccum. Bubble free solution is coated on non-treated casting film coated film is sent to aeration drying oven. Film is cutting into desired shape and size.

1.6.2 Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture.

Finally the melt is shaped into films by the dies. There are certain benefits of the hot melt extrusion.

- Fewer operation units
- Better content uniformity
- An anhydrous process

1.6.3 Solid dispersion extrusion

In this method immiscible components are extruded with drug and then solid dispersions were prepared. Finally the solid dispersions are shaped into films by means of dies.

1.6.5Rolling method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.

Table 3: Examples of marketed oral thin films

Brand name	**Manufacturer/ distributor**	**API (strength)**	**Uses**
Eme film	Delvin formulations pvt ltd	Ondansetron 4 mg	Nausea & vomiting
Listerine cool mint pocket packs	Pfizer	Mint crystals	Mouth freshner
Niquistin stripes	Omega pharma ltd	Nicotine 2.5 mg	Anti smoking
Zupelnz stripes	Monosol Rx	Ondansetron 8 mg	Ondansetron
Spiromont	Monosol Rx	Montelukast 10 mg	Asthma& allergy
Sildenafil citrate film	Alpha pharma health care	Sildenafil 50 mg	Erectile function
Tadalafil stripes	Alpha pharma health care	Sildenafil 20 mg	Erectile function
Vitamin D3	Zim laboratories	Calciferol 2,000 I.U	Calcium supplement
Benadryl	MC Neil consumer health care	Diphenhydramine 25 mg	Antihistamine
Tri aminic	Novartis	12.5 mg	Antiallergic

1.7 EXCIPIENTS GENERALLY USED IN PREPARATION OF FAST DISSOLVING FILMS[6]

Table 4: List of excipients

Ingredients/purpose	Examples	% (W/W)
Water soluble polymers	Cellulose ethers (HPMC, HEC,HPC, and MC), PVC, PVA, gelatin, pullulan, kollicoat IR, tragacanth gum, guar gum, chitin, etc.,	40-50
Plasticizers	Glycerol, PG, PEG	0-20
Disintegrants	Pre gelatinised starch, MCC, crosspovidone, soluble starch	0-40
Preservatives	Salts of edetate (di sodium EDTA)	0.01-1
Saliva stimulating agent	Citric acid, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acid.	2.5-6
Cooling agents	Mono methyl succinate	0.2-0.4
Surfactants	Mono& di glycerides of FA, poly oxy ethylene sorbitol esters	0.5-15
Stabilizing agents	Xanthan gum, locust bean gum and carrageenan	0.1-2
Emulsifying agents	Triethanolamine stearate, Qt.ammonium compounds, acacia, gelatin	0.01-0.7
Thickening gents	MC, CMC	0.01-5
Binding agents	Starch	0.01-2
Sweetening agents	Sucralose, aspartame, acesulfame K, neotame	0-2

1.8 EVALUATION OF THE FILMS[6]

1.8.1 Thickness

The film thickness was measured using a micrometer screw gauge at five points on the film to ensure the uniformity of the film thickness. The mean thickness was calculated from the five points.

1.8.2 Folding endurance test

Folding endurance values reflect the strength of the film prepared.

1.8.3 Weight variation

Ten films were randomly selected and their average was obtained. Individually films were weighed and compared with the average weight for the deviation.

1.8.4 Drug content

Drug content determination of the films is to ascertain whether the required amount of drug loaded in the polymer or not.

1.8.5 Disintegration test

To find out actual time required for disintegration of the film.

1.8.6 Fourier transform infrared spectroscopy studies(FT-IR)

FTIR spectral measurements are useful to find out the interaction between the polymer, excipients and drug if any.

1.8.7 Differential scanning calorimeter studies (DSC)

DSC studies are useful to know the thermal stability of the drug and loaded film.

1.8.8 *In-vitro* dissolution test

Dissolution study was carried out by using a UV spectrophotometer.

1.8.9 *In-vitro* disintegration test

2ml of water was placed in a petriplates with a film on the surface of water. The time taken for the disintegration of the film was measured.

1.9.0 SEM ANALYSIS

The morphological study of oral film was done by the scanning electron microscopy at definite magnification (SEM).

1.9 TASTE MASKING TECHNIQUES[7]

It is estimated that there are about 10,000 taste buds on the tongue, roof of the mouth, cheeks, and throat, and each bud has 60-100 receptor cells. These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Many drugs are unpalatable and unattractive in their natural state. Physiological and physicochemical approaches have been used to prevent drugs from interacting with taste buds, and thus eliminate or reduce negative sensory response.

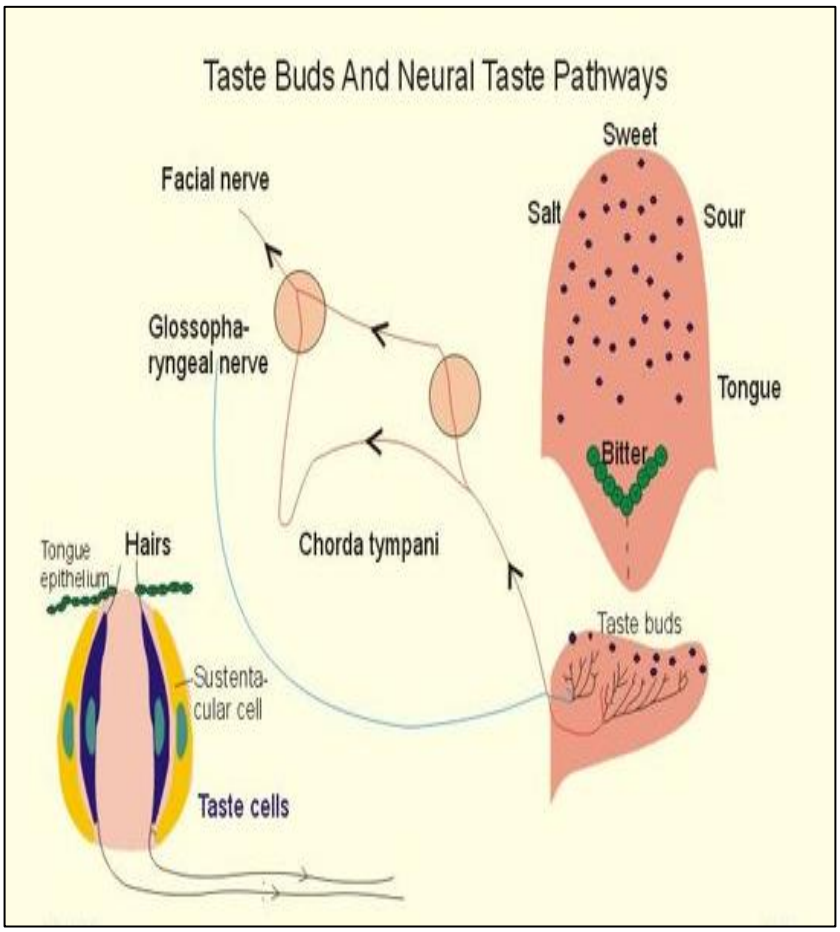

Fig 3: Taste buds and neural taste pathways

Acids evoke sourness, because H^+- receptors in the taste bud. Saltiness is produced by the anions of the inorganic salts. The cl^- receptor is particularly effective in registering saltiness. Our taste buds at the base of the tongue also have bitter-receptors stimulated by many long chain organic compounds. Many alkaloids (quinine, caffeine, and nicotine) also taste bitter. Sweet receptors are stimulated by sucrose, glucose, lactose, maltose, glycerol, alcohol, aldehyde, ketones and organic chemicals. FDDFs disintegrating/dissolve in the saliva and the drug in FDDFs remain in the oral cavity until it is swallowed. Hence, for a drug with bitter taste, taste making becomes critically important in the formulation for maximal patient acceptability. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity.

Oral films also called oral wafers in the related literature are a group of flat films, which are administered into the oral cavity.

1.10 APPLICATION OF ORAL STRIP IN DRUG DELIVERY[7]

Oral mucosal delivery via buccal, sublingual and mucosal route by the use of OTFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleeping difficulties and central nervous disorders.

Dissolvable oral thin films (OTFs) evolved over the fast few years from the confection and oral care markers in the form of breath stripes and become a novel and widely accepted form by consumers for delivering vitamins and personal care products.

1.10.1 Topical applications

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care other applications.

1.10.2 Gastro retentive dosage systems

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could be potentially used to treat gastrointestinal disorders.

1.10.3 Diagnostic devices

Dissolvable films may be loaded with sensitive reagents to allow control release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.

1.11 DIABETES MELLITUS[8, 9]

A group of disease characterized by high levels of blood glucose resulting from defects in insulin protection, insulin action or both.

Diabetes mellitus can be classified into two types,

1. Type 1 diabetes
2. Type 2 diabetes

1.11.1 TYPE I DIABETES[10, 11]

Type 1 diabetes was previously called insulin dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. It develops when the body as immune system destroys pancreatic beta cell, the only cells in the body that make the hormone insulin that regulates the blood glucose. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. It may account for 5-10% of all the diagnosed cases of diabetes.

Risk factors for type 1 diabetes may include auto immune, genetic and environmental factors.

TREATMENT

Insulin therapy.

1.11.2 TYPE II DIABETES[12, 13]

Type 2 diabetes was previously called noninsulin dependent diabetes mellitus (NIDDM) or adult onset diabetes mellitus. It may account for about 90%-95% of all diagnosed cases of diabetes. It usually beings as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.

Type 2 diabetes associated with old age, obesity, family history of diabetes, history of gestational diabetes. Impaired glucose metabolism, physical inactivity, and race ethnicity.

Type 2 diabetes increasingly being diagnosed in children and adolescence.

TREATMENT

Oral hypoglycemic medications.

Table 5: Oral hypoglycemic agents[14]

Drug class	Drug name	Mechanism of action
Biquanides		
Sulphonyl urea's (second generation)	Glimepiride Glipizide Glyburide	Increase insulin secretion by pancreatic β cells
Mateglitinides	Rapeglinides Nateglinides	Increase insulin secretion
Thiozolidinediones (TDZs)	Pioglitazone Rosiglitazone	Increase glucose uptake by skeletal muscle
Alpha glycosidase inhibitors	Agarbose Maglitol	Inhibit carbohydrate absorption in the small intestines
DPP-4 inhibitors	Sitagliptin	Increase insulin secretion by pancreatic β cells and suppress the release of glucogan by pancreatic α cells

Among all the oral hypoglycemic agents for type 2 diabetes mellitus DPP-4 inhibitors plays an important role in diabetes mellitus.

Gliptins represent a novel class of agents that improve beta cell health and suppress glucogan, resulting in improved post-prandial and fasting hyperglycemia.

The function by augmenting the cretin system (GLP-1 and GIP) preventing their metabolism by Dipeptidyl peptidase -4(DPP-4), are they efficacious and also safe.

Aim and Objective

2. AIM AND OBJECTIVE

2.1 AIM

The aim of the present study is to formulate and evaluate the Sitagliptin phosphate fast dissolving oral film by using solvent casting method.

2.2 OBJECTIVE

The objective of the proposed work is

2.2.1 To prepare fast dissolving oral films of Sitagliptin phosphate by using different concentrations of film forming polymers and plasticizers.

2.2.2 The formulations are developed and evaluated for pre-compression parameters such as Solubility, Melting point, Heavy metal content, FT-IR studies and post-compression parameters such as Weight variation, Thickness, Folding endurance, Tensile strength, percentage elongation, Drug content, Assay, Disintegration time, dissolution test and SEM analysis.

2.2.3 To improve the patient compliance.

2.2.4 To get the quick onset of action to relieve the symptoms of hyperglycemia.

Plan of Work

3. PLAN OF WORK

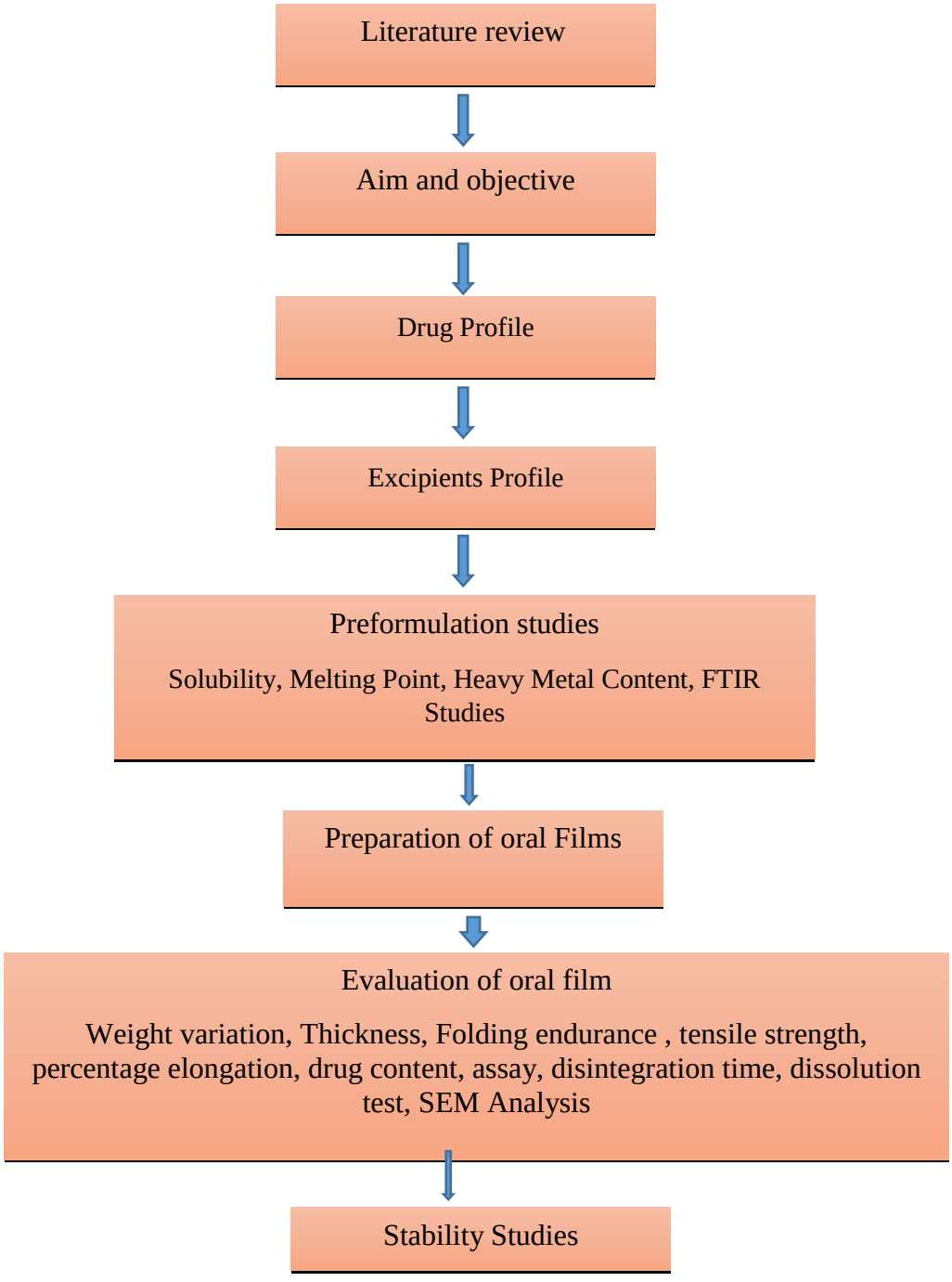

Fig4: Plan of Work

Literature Review

4. LITREATURE REVIEW

Nishi Thakur et.al[2] prepared 'Overview "A novel approach of fast dissolving films and their patients". Fast dissolving drug delivery systems have started gaining fame and acceptance as new drug delivery systems. Which aim to enhance safety and efficacy of a drug molecule by formulating it into a conventional oral dosage form for administration and to achieve better patient compliance. Fast dissolving drug delivery the film is placed on the top or the floor of the tongue. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such case is enhancing drug bioavailability, no risk of chocking, provide good mouth feel. Fast dissolving drug delivery system to overcome this problem difficulty in swallowing tablets/capsules etc. This review article overview the advancement in the oral dosage forms application, formulation consideration, method of preparation, evaluation, marketed product and patented technologies of oral fast disintegrating films.

Arun arya et.al[5] were reviewed 'Fast dissolving oral films: An innovative drug delivery system and dosage form'. Dissolvable oral thin films (OTFs) evolved over the past years from the confection and oral care markets in the form of breath strips and become a novel and widely accepted from by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition technology to ODF formats

G. Kadhe and R.E. Arasan et.al[8] studied as attempt to describe the advances drug delivery of oral hypoglycemic agents, particularly the immediate release formulations of sitagliptin phosphate.

Shelen M colham et.al[9] studied The primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative Atorvastatin diabetes study.

Jigisha patel et.al[10] studied the Dyslipidaemia in diabetes mellitus. The study revealed that statics improved cardiovascular out comes in people with diabetes mellitus. Atorvastatin 10mg daily significantly reduced cardiovascular events at 3.9 years in people with type 2 diabetes without cardiovascular disease.

Salim Bastaki et.al[14] were studied The diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses tissue or vascular damage ensures leading to serve diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus diabetes covers a wide range of heterogeneous diseases.

Wale kiran K et.al[17] were formulated 'Formulation and development and in-vitro evaluation of immediate release tablet of sitagliptin phosphate monohydrate. This investigation undertaken with an aim to develop pharmaceutically equivalent, stable, cost effective and quality improved formulation of sitagliptin phosphate monohydrate immediate release tablets. Wet granulation method was adopted to prepare the sitagliptin phosphate monohydrate immediate release tablets by using micro crystalline cellulose, lactose as diluents, crosspovidone and sodium starch glycolate as super disintegrant in different concentration (2-8%) to prepare (S1-S9) batches.

Tablets were prepared and evaluated for hardness, friability, weight variation, content uniformity, and disintegration time and in-vitro drug release.

Abbaraju prasanna Lakshmi et.al[18] was prepared 'Formulation and evaluation of taste masked orally disintegrating tablets of sitagliptin phosphate monohydrate'. The unpleasant taste of sitagliptin phosphate monohydrate with mannitol by co-grinding method and formulate oral disintegrating tablet by direct compression method. Drug-mannitol complxes were taken in 1:1, 1:1.5 and 1:2 ratio and tested for in vitro and in vivo bitter masking capacity of mannitol, drug content and molecular property. Different super disintegrants like crosscarmellose sodium, sodium starch glycollate and crosspovidone was used as disintegrating agents. The prepared tablets were characterized for tensile strength, wetting time, water absorption ratio and in vivo disintegration time.

Desai P et.al[26] were formulated 'Formulation and evaluation of fast dissolving film of Domperidone'. Domperidone is a specific blocker of dopamine receptors solvent casting method was used for preparation of fast dissolving film. Various film forming polymers were evaluated for selection of suitable polymer. Different polymers like maltodextrin, PVA and different grades of HPMC like HPMCE5 LV, HPMC E15 LV and HPMC E3 LV were used in the study for selection of polymers. Amongst them HPMC E3 LV, HPMC E5 LV was selected as film forming polymers and propylene glycol was used as plasticizer. For solubility enhancement inclusion complex from β cyclodextrin was prepared by kneading method. Films were evaluated for physical and mechanical properties, drug content, disintegration time, in vitro dissolution study. Prepared films showed satisfactory physical and mechanical properties. Drug-excipients interaction study (IR), differential scanning calorimetry (DSC), drug content, disintegration time and in vitro dissolution were also acceptable. 3^2 factorial design were used for optimization of film formulation. Batch F4 was fund to be

optimized film formulation which has 35.33 sec disintegration time, tensile strength 2.180 N/cm^{2,} drug release 75.26% after 15 min. accelerated stability studies on the promising formulations indicated that there were no significant changes in drug content, *in vitro* disintegration time, tensile strength, *in vitro* dissolution and surface pH.

Buchi N.Nalluri et.al[27] was prepared 'Development and evaluation of mouth dissolving films of sumatriptan succinate for better therapeutic efficacy'. Sumatriptan succinate (SUM) to enhance convenience and compliance to the elderly and pediatric patients for better therapeutic efficacy. Film former, HPMC along with film modifier/solubilizing agent, PVPK 30 and sodium lauryl sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for in-vitro dissolution characteristics, in vitro disintegration time, and their physic-mechanical properties. MDFs with 13% (w/w) of HPMC E15. MDFs with PVP K 30 and SLS gave superior dissolution properties when compared to MDFs with SLS. Overall, SUM MDFs showed good mechanical properties like tensile strength, folding endurance and% elongation and dissolution properties. These results suggest that the HPMC is an excellent film former which gives rapid drug release.

P. Narayana raju et.al[28] were prepared 'Formulation and evaluation of fast dissolving films of Loraditine by solvent casting method'. Rapidly dissolving films of loratidine were developed using low viscosity grades of HPMC as film forming polymers. HPMC is a water soluble synthetic polymer which was used as film former form many years. The films of loratidine were prepared by solvent casting method using Di-chloromethane and methanol as solvents. The prepared films were evaluated for drug content, weight variation, thickness and in vitro and in vivo disintegration time. Loratidine is moderately bitter drug,

taste masking was achieved by use of sweeteners, flavors and citric acid. Type of flavor significantly affected the taste masking property. The in-vitro and in vivo disintegration time of the optimized formulation was found to be below 29 seconds and 24 seconds respectively. The prepared films exhibited good integrity and thickness. In vitro dissolution studies were performed as per the FDA dissolution guidelines for about 10 minutes, the optimum formulation released complete drug within 4-6 minutes. DSC and FT-IR studies showed no drug polymer integration.

Komaragiri sasi deepthi et.al[29] was investigated 'Formulation and characterization of Atenolol fast dissolving films'. Atenolol is a β selective adrenergic antagonist used as antihypertensive agent. Films were prepared using film forming polymer like HPMC E5 (F1-F8) and tween 80 is added to the formulation from F5-F8 by solvent casting technique with the help of PEG 400 as plasticizer and glycerine as sweetening agent. FT-IR analysis was performed to study the interaction between the drug and polymer. The films were evaluated for weight variation, surface pH, folding endurance, drug content, dissolving time, disintegration time, and in-vitro dissolution studies. Based on the evaluation parameters F4 containing drug: polymer (1:4) ratio showed optimum performance and marked increase in releasing of drug 92.34%, though F8 formulation has maximum drug release as it has less tensile strength. It can be concluded in the study that mouth dissolving film can be potential novel drug dosage form for poorly water soluble drugs.

Pavani.S et.al[30] prepared 'Formulation development and evaluation of taste masked oral disintegrating films of Atenolol'. Atenolol is β1- selective adrenergic blocker and widely used in the treatment of hypertension and angina pectoris. It has a bioavailability of 40-50%. The main objective of the study was to formulate taste masked oral disintegrating films of Atenolol to achieve a

better dissolution rate by improving the bioavailability of the drug and providing quick onset of action there by enhancing patient compliance. Oral disintegrating films prepared by solvent casting method using film forming polymer HPMC E15 in different ratios. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time and *in-vitro* dissolution studies and taste mask studies on healthy human volunteers. Among all, the formulation F3 containing HPMC E15 (drug : polymer of 1:2) was found to be the best formulation which releases 99.89% of the drug within 20 minutes and disintegration time is 15.3 sec.

Raghavendra rao et.al[31] were developed 'Design and development of fast dissolving thin films of losartan pottasium'. The fast dissolving films of losartan potassium were prepared by solvent casting method using film forming polymer HPMC 15 and 50 cps and PEG is used as a plasticizer. The electron microscopy showed that the films are clear, colorless with smooth surface and little pores, without any scratches on the films. All the films prepared were evaluated for physical appearance and surface texture, weight uniformity of films, thickness of the films, folding endurance, surface pH, drug content uniformity and in-vitro disintegration time of films. All the results were found to be satisfactory. The $t_{50\%}$ and $t_{90\%}$ values decrease with increase in the concentration of SSG, CCS and CP. The rapid increase of in dissolution of losartan potassium with the increase in CCS. Among all the film formulation FA2 and FA8 (6% CCS, HPMC 15 and 50 cps) were found to be promising and showed a disintegration time of 36 and 32 seconds, respectively and 50% of drug released in 9.74 and 8.19 minutes, and 90 5 of drug release in 18.00 and 17.12 minutes respectively. Based on the above results it can be concluded that the fast dissolving oral film of losartan potassium may produce the rapid action there by enhance the absorption by avoiding the first pass effect.

Talele swati G et.al[32] was prepared 'Formulation and evaluation of mouth dissolving film of Almotriptan malate'. The present study was aimed to formulate and evaluate mouth dissolving films of almotriptan malate using polymers HPMC E-15 and HPMC E-4 and gelatin as the film forming agents. Formulation batches formulated using 3^2 full factorial designs. The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. PEG 400 was incorporated as plasticizer to improve flexibility of films. Aspartame as sweetener. Sodium starch glycolate used as disintegrant. An attempt was made to prepare mouth dissolving films of almotriptan with the purpose of developing a dosage form for quick onset of action. The films were prepared by solvent casting method. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content, surface pH, percentage elongation and tensile strength and gave satisfactory results. The formulation were subjected to disintegration, in-vitro drug release. The FTIR studies revealed that no physicochemical interaction between excipients and drug. Melt in mouth films of almotriptan containing single polymer HPMC E-15 showed best results, in terms of tensile strength (1.76±0.11), percentage elongation (36.63±0.288%), folding endurance (>300), *in-vitro* disintegration time (26.01±0.11 sec), surface pH (6.20±0.001), thickness (0.096±0.011 mm) and percentage content uniformity (97.23±0.091). satisfactory dissolution profile was obtained with maximum release of 96% of drug within 120 sec. The stability studies showed that there was no appreciable change in parameters when stored at three different temperatures.

Kranthi kumar.v et.al[33] developed 'Formulation and evaluation of carvedilol fast dissolving sublingual films'. Carvedilol, a nonselective β blocker is an antihypertensive drug which has oral bioavailability of 25-35% with conventional dosage forms due to first pass metabolism. The present study

investigated the possibility of developing carvedilol fast dissolving sublingual films allowing fast, reproducible drug dissolution in the oral cavity, thus bypassing first pass metabolism to provide rapid onset of action of the drug. The fast dissolving films were prepared by solvent casting method. Low viscosity grade of HPMC E3 and HPMC E5 were used as film forming polymers. In this study tween 80 was used as solubilizing agent as well as plasticizer. All the film formulations F1-F9 were evaluated for their thickness, weight variation, tensile strength, percentage elongation, folding endurance, in-vitro disintegration, drug content, in-vitro drug release and ex-vivo permeation studies. Disintegration time showed by the formulations was found to be in range of 25-50 sec. Formulations F7 was chosen as the best formulation which showed 96.65 % in-vitro drug release within 5 minutes and 62.36% ex-vivo drug permeation within 60 mins. The film showed an excellent stability at least for 45 days when stored at 40°c and 75% relative humidity.

Deepthi et.al[34] was prepared 'Formulation and evaluation of fast dissolving oral films of Zolmitriptan'. The present study was aimed to formulate and evaluate fast dissolving oral films of Zolmitriptan using sodium alginate, xanthan gum and sodium starch glycolate, guar gum. The suitable plasticizer and its concentration were selected on the basic of flexibility, tensile strength and stickiness of the film. The films are prepared by solvent casting method and characterized by UV, FTIR studies. The films were evaluated for disintegration time, Folding endurance, Tensile strength, Mouth dissolving time, Thickness, content uniformity and *in-vitro* dissolution studies. The F5 formulation has given 98.5% drug release within 6 minutes and has a tensile strength of 1.80 MPa.

Ali MS et.al[35] was formulated 'Formulation and evaluation of fast dissolving oral films of Diazepam'. Oral films rapidly along with drug in mouth and

majority of the drug is absorbed through buccal/oral mucosa into systemic circulation avoiding first pass metabolism. Diazepam is an antiepileptic drug which is normally administered by intramuscular route or as rectal suppository in acute conditions of seizure emergencies. Oral films were prepared by solvent casting method using HPMC E3, E5, and HPMC E15 as a film formers and propylene glycol, PEG 400 as plasticizers and evaluated for mechanical properties, disintegration and in-vitro drug release. The optimized (F4A) formulation (HPMC E5 and PEG 400) exhibited drug release of 99.89 %in 15 minutes which was significantly high when compared to marketed tablet valium (68.81 %).

Alka tomar et.al[36] was formulated 'Formulation and evaluation of fast dissolving oral film of Dicyclomine as potential route of buccal delivery'. The aim of the study is to formulate and evaluate the (FDOF) of an anticholinergic drug (Dicyclomine) and improved bioavailability of drugs as compared to conventional solid oral dosage forms. Oral films were prepared by using HPMC, PVA, Eudragid RL-100, combination of two polymers and other excipients. Films were prepared by solvent casting method. Films were evaluated for mechanical properties, morphology study, swelling properties, disintegration time, dissolution time, and in-vitro drug release. X1 formulation shows maximum *in-vitro* drug release 93.88%, following first order kinetics (r^2 =0.9915). The release exponent 'n' was found to be for X1 is 0.4487, which appears to indicate that the drug release was controlled by first order release.

Anjum pathan et.al[37] developed 'Formulation and evaluation of fast dissolving film oral film of Promethazine hydrochloride using different surfactant'. The aim of the present study is to formulate and evaluate the fast dissolving oral film of promethazine hydrochloride. Promethazine hydrochloride as a strong antihistamine which are used to reduce nausea, motion sickness and improved

bioavailability of drugs as compared to conventional solid oral dosage forms. The films were prepared HPMC E15 as a film base synthetic polymer and PEG 400 as a plasticizer by solvent casting method. SLS and MCC used as surfactant in different concentration. Sucrose used as sweetening agent and strawberry as a flavoring agent. Films were found to be satisfactory when evaluated for thickness, weight variation, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of the all films was found to be neutral or minor charge. Films *in-vitro* drug release studies also done by using dissolution apparatus. The *in-vitro* drug release in optimized formulation F2 was found to be 14.36% in 2 min. the optimized formulation F2 also showed satisfactory pH, drug content (97.41±0.54), effective in vitro drug release (96.03±0.68% in 16 min), disintegration time of 9 seconds and satisfactory stability. The promethazine hydrochloride fast dissolving oral film was formulated. The given film disintegrates within 9 seconds which release drug rapidly and gives action.

Kamalesh upreti et.al[38] designed 'Formulation and evaluation of mouth dissolving films of Paracetamol'. In the resent study, mouth dissolving films of paracetamol were prepared by solvent casting method. Several formulations were developed by varying polymer (HPMC) and plasticizer (glycerol) concentrations. Sweetening and flavoring agents were also added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content. In the present study, each mouth dissolving film was 2×3 cm in size and contained 125 mg paracetamol (PCM). Thickness of the films were approximately 2mm. the strip disintegrated completely within 4 mins. In-vitro dissolution studies were carried out in distilled water as well as in simulated salivary fluid (pH 6.8). The optimized formulations showed 92% drug release

within 30 min. The prepared stripes seem to be an attractive alternative to conventional marketed formulations.

Mital.s.panchal et.al[39] formulated 'Formulation and evaluation of mouth dissolving film of Ropinirole hydrochloride by using pullulan polymers'. The films of ropinirole hydrochloride were prepared by using polymers such as pulllan and PEG 400 as plasticizer, by a solvent casting method. Formulation batches were formulated with the help of 3^2 full factorial designs. The fast dissolving oral films were prepared using optimal design and numerical optimization technique was applied to find out the best formulation. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content, surface pH, percentage elongation and tensile strength and gave satisfactory results. The formulation were subjected to disintegration, in-vitro drug release tests and stability study. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. A marked increase in the % drug release was exhibited by mouth dissolving films of Ropinirole hydrochloride containing pullulan as a polymers at 60 sec., when compared to other polymer films. Mouth dissolving film of Ropinirole hydrochloride containing as pullulan showed 99.48±0.18% drug release at 60 sec. mouth dissolving films of Ropinirole hydrochloride containing pullulan showed better tensile strength (9.67±0.064g/mm^2), percentage elongation (21.59±0.29 %), folding endurance (88.00 1.00 no. of folds), in-vitro disintegration time (20.33±0.57 sec), surface pH (6.60±0.10 pH), thickness (0.07±0.01 mm) and percentage content uniformity (99.53±0.37 %). Stability studies revealed that optimized formulation was stable. Mouth dissolving films of Ropinirole hydrochloride can be considered suitable for clinical use in the treatment of parkinson's disease and rest leg syndrome, where a quicker onset of action for a dosage form is desirable along with the convenience of administration.

Thonte S.S et.al[40] were formulated 'Formulation and Evaluation of Oral Dissolving film of glibenclamide'. The aim of the present study was to formulate fast dissolving films of Glibenclamide using HPMC K-15, HPMC E-15 HPMC K-100 PEG (400) as a plasticizer, tween 80 as a surfactant, and citric acid as a salivary agent. Glibenclamide solid dispersion of PEG 6000 is dispersed in the polymer solution. Films were prepared by the solvent casting method and found to sati\sfy the mouth dissolving time and other film parameters. The film instantly gets wet by saliva, rapidly hydrates, adheres to a tongue and rapidly disintegrates and dissolves to release the drug for the oro-mucosal absorption or allow for gastrointestinal absorption to be achieved when swallowed. The formulated films exhibited acceptable films endurance. The time required films exhibited acceptable films endurance. The time required for the film to dissolve and release 26 seconds and 2 minutes respectively. It can be concluded from the study that the oro-flash release film can be a potential novel drug dosage form for poorly water-soluble drugs.

DR. D.Nagendrakumar et.al[41] were designed 'Formulation and evaluation of fast dissolving oral films of Metoprolol succinate'. The key is to develop successful oral film by solvent casting method and selected the right compatible excipients using FTIR studies. Oral films were fabricated using HPMC E5 and HEC polymer. The prepared films were evaluated for organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity, surface pH, disintegration time and *in-vitro* dissolution studies. The formulation F5 has disintegration time of 7 seconds and is more promising and showed drug release of 98% after 5 minutes; hence formulation F5 was selected as best formulation.

Poonam A.padamwar et.al[42] was prepared 'Formulation and evaluation of fast dissolving oral films of Bisoprolol fumarate'. The films were prepared by using

polymers such as HPMC and maltodextrin, plasticizer such as PEG 400, by a solvent casting method. The formulated fast dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content, surface pH, percentage elongation and tensile strength and gave satisfactory results. The formulation were subjected to disintegration, in-vitro drug release. The *in-vitro* disintegration time of the optimized batch F4 was found to be 20 sec. The optimized batch was found be stable for 1 month under specified stability conditions.

Sarita rana et.al[43] was developed 'Formulation and evaluation of Domperidone fast dissolving film by using different polymers'. Developing a fast dissolving delivery system releasing domperidone concomitantly in stomach for treating vomiting and motion sickness. Domperidone FDFS was prepared by solvent casting principle. Different concentration of film forming polymer i.e. domperidone with and without solubilizing agent tween 80 had better. Korsmeyer-peppas model was found to be fit kinetic in which all formulation showed good linearity (R^2: 0.906 to 0.989), with slope (n) values ranging from 0.655 to 0.981. In korsmeyer-peppas model, 'n' is the release exponent indicative of mechanism of drug release. The 'n' values ranged from 0.5-1.0 indicate anomalous transport (non-fickian) diffusion where drug release is both diffusion and swelling controlled.

Julie Mariam Joshua et.al[44] were designed 'Formulation of propranolol hydrochloride oral thin films for migraine prophylaxis'. Propranolol Hcl is a non –selective β adrenergic antagonist completely absorbed from the GIT tract. The purpose of developing these dosage form is to reduce the dose by bypassing its first pass metabolism. Films were prepared from F1-F6 by solvent casting technique. Pullulan was selected as polymer because of its good water solubility and propylene glycol as plasticizer. PVP was selected as disintegrant, citric acid

as saliva stimulating agent, mannitol as sweetening agent and menthol was used as flavoring agent. The compatibility of the drug in the formulation was confirmed by FTIR and DSC. Formulated films were subjected to various evaluation parameters. Based on the evaluation parameters, F4 has disintegration time of 47 sec and showed promising drug release of 93% after 20 min. SEM of F4 showed smooth surface and little pores. The stability study proved that the formulation F4 was found to be stable in both refrigerator and room temperature. Ex-vivo permeation study of F4 showed 91% of drug permeation through goat oral mucosa: hence formulation F4 was selected as best formulation.

Farhana sultana et.al[45] designed 'Preparation and evaluation of fast dissolving oral thin films of Caffeine'. Films were prepared by using HPMC 15 cps, sodium alginate& kollicoat IR white in various proportions. Total nine formulations were prepared and conducted various physicochemical evaluations including FT-IR and in-vitro dissolution studies from the trinocular microscopic images. It appears that kollicoat IR white is more porous which may be due to the characteristic behavior of graft of co polymer was reflected in its lowest disintegration time (12 sec) and its cumulative percentage release was 99.86% within 240 seconds. Films in formulation F1 prepared with HPMC were very flexible, smooth and its in-vitro disintegration time was 13 seconds. Its cumulative percentage drug release was 100% within 120 seconds which is remarkable in comparison to other formulations.

Thonte S.S et.al[46] was prepared 'Formulation and evaluation of oral fast dissolving film of Glipizide'. Films were formulated using HPMC K-15, HPMC E-15, HPMC K-100 and PEG 400 was used as plasticizer to give flexibility to the films. In FT-IR study inter was drug and excipients. Three blank films were selected for the in comparison of drug. After characterization the drug loaded

films and studied their dissolution time and in-vitro drug release studies, among all the formulations (F1-F10) F3,F4,F5,F6,F7&F9 has selected the best formulation as its disintegration and dissolution time was less and it releases the drug to a greater extent from 93% to more than 100% in 10 minutes. From F9 was selected best formulation as its disintegration and dissolution time was less. And released drug to a greater extent compared to other formulation. Therefore fast dissolving oral films can play an important role in oral drug delivery. Drug loaded films with both the polymers were stable under 40°C/75%RH conditions.

Pravin kumar sharma et.al[47] developed et.al 'Development and evaluation of fast dissolving oral film of poorly water soluble drug Felodipine'. Solid dispersions of was prepared using solvent evaporation method using PVP K30 as hydrophilic polymeric carrier in different proportions. Felodipine FDFs were prepared using solvent casting method. The concentration of HPMC E5 as film forming polymer, propylene glycol as plasticizer and crosscarmellose as disintegrating agent and selected as response variables. Evaluated weight variation, thickness, drug content, folding endurance, surface pH, moisture content, percentage swelling, percentage elongation, tensile strength, in-vitro disintegration, in-vitro dissolution, stability study, surface morphology using SEM, ex-vivo permeation study and in-vivo pharmacokinetic study. FTIR and DSC analysis revealed that the compatibility between the drug and excipients. Felodipine FDFs indicated disintegration time of 22.84±0.33 and in-vitro percentage drug dissolution.

Rubia Yasmeen et.al[55] formulated 'Preparation and evaluation of oral fast dissolving films of citalopram hydro bromide'. Citalopram is an antidepressant also used for mood disorders such as anxiety and obsessive and compulsive disorder. Fast dissolving films of citalopram hydro bromide were prepared by solvent casting technique. HPMC E5 was selected as polymer because of its

good water solubility. Propylene glycol as plasticizer and sorbitol as sweetener were used in the formulation. The compatibility of the drug in the formulation was confirmed by FTIR studies. Surfactants by their wetting ability further reduce disintegration time and enhance the drug release in mouth dissolving films, so tween 80 at concentrations of 10% w/w of polymer concentration was included some formulations. By varying the concentration of polymer and surfactant, four formulations F1, F2, F3 and F4 were formulated. The prepared films were evaluated for there by physic -chemical parameters like folding endurance, weight variations, thickness, surface pH, dissolving time and disintegration time. Estimation of drug content of films was performed and the results were satisfactory. *In vitro* dissolution studies revealed higher drug release from formulations F3 and F4. The order of drug release was found to be F3>F4>F1>F2.

Drug Profile

5 DRUG PROFILE

SITAGLIPTIN PHOSPHATE[15, 16]

STRUCTURE

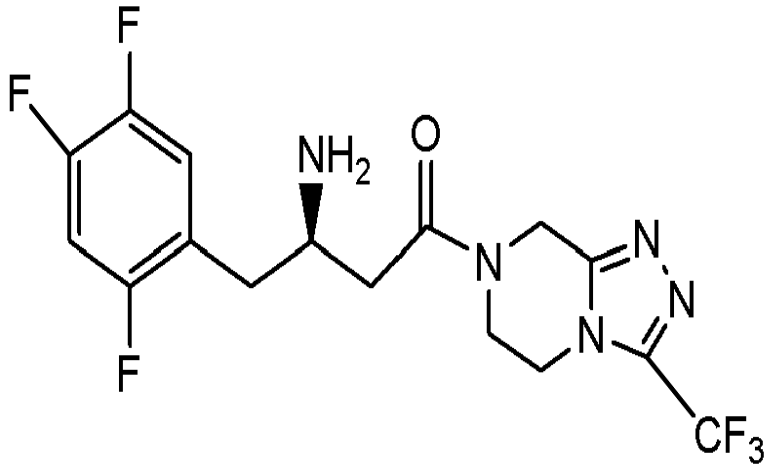

Fig 5: structure of Sitagliptin phosphate

IUPAC NAME

(R) -4-oxo-4-[3-(tri fluro methyl)-5,6-dihydro[1,2,4] trizolo [4,3-a] pyrazin-7(8H)-yl-]-1-(2,4,5-triflurophenyl) butane-2-amine.

CHEMICAL DATA[17]

Formula : C16H15F6N5O

Molecular mass : 407.314 g/mol

Molecular weight : 532.32

Melting point : 205-206°

Physical state : It a white to off-white, crystalline non-hygroscopic powder.

MECHANISM OF ACTION[18]

Sitagliptin works to competitively inhibit the enzyme Dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretin GLP-1 and GIP, gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, there are able to increase the secretion of insulin and suppress the release of glucogan by the alpha cells of the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, amount of insulin released and glucogan suppressed diminishes, thus tending to prevent an overshoot and subsequent low blood sugar (hypoglycemia).

PHARMACOKINETICS[19]

Absorption

Sitagliptin is rapidly absorbed, with a 100 mg dose reaching a C_{max} of 950 nm in 1-4 hr ; AVC was 8.52 MC ^{M}. The bioavailability is approximately 87%.

Distribution

Vd is approximately 198L. Plasma protein binding is 38%.

Metabolism

Metabolism by CYP 3A4 and, to a lesser degree, CYP 2C8.

Elimination

Terminal half -life is approximately 12.4 hr and renal clearance is approximately 350 mL/min. Approximately 13 is excreted in the feces and 87% in the urine via active tubular secretion (79% as unchanged drug). Sitagliptin is a substrate for organic anion transport.

DRUG INTERACTION

Cyclosporin:

Sitagliptin phosphate plasma concentrations may be increased modestly (approximately 68 %) which is not expected to be clinically important.

Digoxin:

Digoxin plasma concentrations may be increased slightly (approximately 18%); no dosage adjustment is recommended.

Insulin, Sulphonylureas (e.g tolbutamide)

A lower dose of insulin or sulphonyl urea may be needed to reduce the risk of hypoglycemia.

DOSAGE AND ADMINISTRATION[20]

Adults

PO 100 mg once daily.

Renal function impairment

Adults moderate renal impairment (Cr Cl 30 to less than 50 ml/min or approximately serum creatinine levels of more than 1.7 upto 3 mg/dl in men and more than 1.7 upto 2.3 mg/dl in women).

PO 50 mg once daily

Severe renal impairment (Cr Cl less than 30 ml/min or approximate serum creatinine levels of more than 3 mg/dl in men and more than 2.5 mg/dl in women).

PO 25 mg once daily

ESRD requiring hemodialysis or potential dialysis.

PO 25 mg once daily

Administer without regard to the timing of hemodialysis.

Excipients Profile

6. EXCIPIENTS PROFILE

6.1 HPMC[21]

Structural formula:

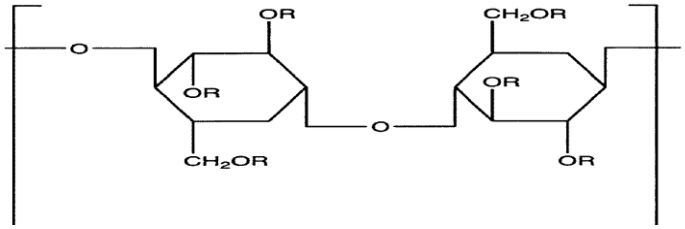

Fig 6: structure of HPMC

Chemical name : Cellulose hydroxyl propyl methyl ether**.**

Chemical data

Molecular mass : $OCH_2CH\ (OH)\ CH_3$

Molecular weight: 10,000-1500000

Melting point : 190-200°C

Physical state : HPMC is an odorless & tasteless or creamy white fibrous or granular powder.

Solubility:

Soluble in cold water, forming a viscous colloidal in soluble in hot water, chloroform, ethanol, dichloromethane, mixtures of water &alcohol.

Incompatibilities:

Incompatible with some oxidizing agents, organic ions to form insoluble

precipitates.

Stability and storage conditions:

It is a stable, although it is hygroscopic after drying.

Stored in well closed container, in a cool & dry place.

Functional category

Bio adhesive material, coating agent, controlled release agent, film former, emulsifier, solubilizing & stabilizing agent, tablet binder, thickening agent.

Application of pharmaceutical formulation/ Technology

- It is widely used in oral, ophthalmic, nasal &topical pharmaceutical formulations.
- Tablet binder in film coating and as a matrix in extended release tablet formulations.
- In liquid orals which is used as a suspending or thickening agent.
- Lower viscosity grades are used in aqueous film coated solution, while higher viscosity grades are used with organic solvent.
- It is also used in cosmetic and food products.

6.2 PROPYLENE GLYCOL[21]

Structural formula:

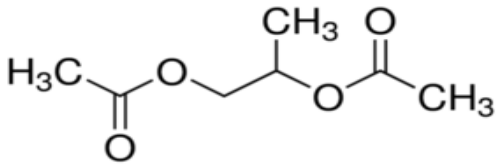

Fig 7: structure of propylene glycol

IUPAC NAME: 1, 2- dihydroxy propane, E1520; 2- hydroxyl propanol.

Chemical name

1, 2-propane diol

(-)-1, 2 propane diol

(+)- 1, 2 propane diol

Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Typical properties

Boiling temperature : 188 c

Density : 1.038 g/cms at 20 c

Flammability : upper limit, 12.6%v/v in air; lower limit, 2.6% v/v in air.

Melting point : 59°C

Solubility : with acetone, chloroform, ethanol (95 %), water.

Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

Stability and storage conditions

At cool temperatures, propylene glycol is stable in a well closed container, but at a high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin or water; aqueous solutions may be sterilized by autoclaving.

Functional category:

Antimicrobial preservative, disinfectant, humectant, plasticizer, solvent, stabilizing agent, water –miscible co solvent.

Application in pharmaceutical formulation or technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parendral and nonparendral pharmaceutical formulation. It is a better general solvent glycerine and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and B), most alkaloids, and many local anesthetics. It is commonly used as a plasticizer in aqueous film-coating formulations.

6.3 POLYETHYLENE GLYCOL[21]

Structural formula:

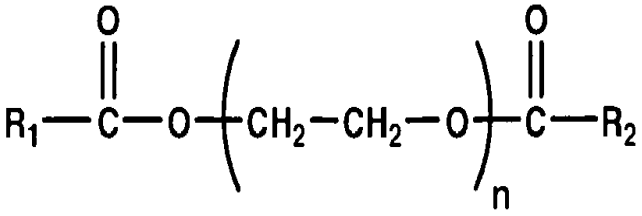

Fig 8: Structure of PEG

IUPAC name : α- hydro- -hydroxy poly (oxy-1, 2, ethane diyl)

Description : PEG occurs as clear, colourless or slightly yellow coloured, viscous liquids.

Typical properties

Density : 1.120 g/cm^3

Melting point : 37-40 C°

Solubility :

All types of PEG soluble in water and miscible in all proportions with other PEG. PEGs are soluble in acetone, alcohol, benzene, glycerine, & glycol.

Incompatibilities :

It may be incompatible with some colouring agents. It reduces the antibacterial activity of penicilins. The preservative effect of parabens may also be impaired to binding with PEG.

Stability and storage conditions

PEG are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic.

Functional category:

Ointment base, Plasticizer, Solvent, Suppository base, Tablet & Capsule lubricant.

Application in pharmaceutical formulation or technology

Poly ethylene glycol is used in pharmaceutical formulations including Parendral, topical, ophthalmic, oral & rectal preparation. It has used biodegradable polymeric matrices used in controlled release systems.

6.4 CITRIC ACID[21]

Structural formula

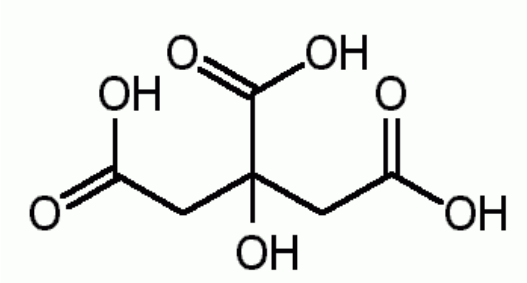

Fig 9: Structure of citric acid

Chemical name : 2- hydroxy-1, 2, 3- propane tricarboxylic acid

Chemical data

Molecular formula : $C_6H_8O_7.H_2O$

Molecular mass : 210.14

Melting point : 100°C

Physical state : Colorless, white crystalline, efflorescent powder. Odorless & has a strong acidic taste.

Solubility :

Soluble in ethanol (95%), water, sparingly soluble in ether.

Stability and storage condition:

Citric acid loses water of crystallization in dry air or when heated about 40°C. It is slightly deliquesant in moist air.

Citric acid anhydrous material should be stored in airtight containers in a cool & dry place.

Functional category:

Acidifying agent, antioxidant, buffering agent, chelating agent, flavor enhancer, preservative.

Applications in pharmaceutical formulation /Technology

- Citric acid is used in pharmaceutical formulations and food products. It also has been used to adjust the pH of the tablet matrices in enteric coated formulation for colon-specific drug delivery.
- It is used in the preparation of effervescent granules, while anhydrous citric acid is used in the preparation of effervescent tablets.
- Improve the stability of spray dried insulin powder in inhalation formulation.
- In food products, used as flavor enhancer for its acidic taste.
- Sequestering agent.
- Antioxidant synergist.

6.5 SACCHARIN SODIUM[21]

Structural formula

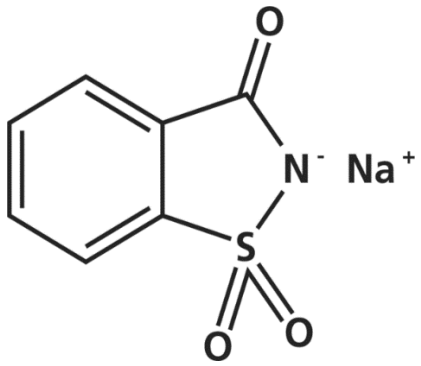

Fig 10: Structure of sodium saccharin

Chemical name : 1, 2 –benzisothiazol-3 (2H) –one 1, 1-dioxide, sodium salt.

Description : White, odorless, efflorescent crystalline powder.

Chemical data:

Formula : C7H4NNaO3S

Molecular mass : 205.16

Density : 0.8-1.1 g/cm^3

Melting point : Decomposes when heating.

Physical state : White, odorless, efflorescent crystalline powder.

Solubility:

Soluble in buffer solution, ethanol, ethanol (95%), propylene glycol, propan-2 -ol

& water.

Incompatibilities:

Saccharin sodium does not undergo Millard browning.

Stability and storage conditions

Stable under normal range of conditions employed in formulation only. When it is exposed to a high temperature (125°C) at low pH for over 1 hour significant decomposition occur.

Functional category

- Sweetening agent
- Application of pharmaceutical formulation/Technology
- It is used as sweetening agent in beverages, food products, table top sweeteners and pharmaceutical formulation such as tablets, powders, medicated confectionary, gels, suspension, liquids and mouthwashes.
- Also used in vitamin preparations.
- Injection of sodium saccharin has been used to measure the arm-tongue circulation time.

Methodology

7. METHODOLOGY

7.1 MATERIALS AND METHODS

Table 6: List of materials

Material	Manufacturer
Sitagliptin phosphate	Dr. Reddy's laboratory
HPMC E15	Accent microcell industries
HPMC E50	Symonds pvt ltd
PEG 400	BASF
Propylene glycol	Spectrum chemicals
Sodium saccharin	Aptuit laurus ltd

Table 7: List of Equipments

Name of Instrument	Model and Manufacturer
Digital balance	Mettler Toledo PR203
Hot air oven	Thermolab
UV Spectrometer	Lab india UV 3000
Dissolution test Apparatus	Lab india D5 8000
Micrometer screw gauge	Mitutoyo, china
Disintegration test apparatus USP	Electro Lab
pH meter	Electro Lab
Stability chamber	Thermo lab Pvt ltd

7.2 PREFORMULATION STUDIES[22-25]

Preformulation may be described as the stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequesant stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients on their compatibility.

7.2.1 Solubility[26, 27]

Solubility is expressed in terms of parts per million of solvent in which 1g of solid is soluble. Solubility of the powder in different solvents like water, ethanol etc was determined at 20°c.

7.2.2 Heavy metal content[28, 29]

The part of Lead per million parts of powder was examined by comparing sample solution with 10 ppm lead standard solution for 2 gm material.

7.2.3 Melting point[30]

The melting point was carried out by using capillary tube method.

7.2.4 Compatibility Studies[31-33]

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of sitagliptin phosphate was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. Then the spectrum of dried mixture of drug and Pottasium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

7.3 FORMULATION DEVELOPMENT OF SITAGLIPTIN PHOSPHATE ORAL FILM[34-36]

Table 8: Formulation trials

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sitagliptin phosphate (g)	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625
HPMC E15 (g)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E50 (g)	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 400 (g)	1.5	1.25	1.0	-	-	-	-	1.25	-
Propylene glycol (ml)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid (g)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium saccharin (g)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Flavor (g)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Distilled water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Fig 11 : Fast Dissolving Film

7.3.1 PROCEDURE[37-40]

The water soluble polymers and plasticizers were dissolved in distilled water. The solution is stirred up for 2 hrs in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed together. Finally the solution is casted on a suitable petriplate to form a film. The plates were kept in a hot air oven at 60° c for 1 hour. The dried film was gently separated from glass plate and cut into a desired sizes.

7.3.2 Dose calculations

Length of glass plate =10 cm.

Width of glass plate =10 cm.

Area of the plate =100 cm^2.

No. of 4 cm^2 films present whole plate =100/4 =25 films.

Each films contains 25 mg of drug.

25 films contain 625 mg drug (25×25).

Labelled claim= 25 mg

7.3.3 Standard Graph of Sitagliptin Phosphate[41-43]

Stock solution was prepared by 50 mg of sitagliptin phosphate in 100 ml of water. From this stock solution 10 ml was withdrawn and diluted upto 100 ml using water. Calibration curve was prepared by using different concentration (20 µg/ml-100 µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 267 nm.

7.4 EVALUATION OF ORAL FILM[44]

7.4.1 Thickness[45]

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5 %.

7.4.2 Weight variation[46]

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.

7.4.3 Folding endurance[47]

To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between100-150.

7.4.4 Percentage elongation[48]

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

7.4.5 Tensile strength[49]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

7.4.6 *In-vitro* disintegration[50, 51]

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva.

Petri dish method

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely.

7.4.7 *In-vitro* dissolution[52]

900 ml of o.1 N HCL was used as a media, at was maintained at 37 +0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. 5 ml of the sample were taken every 2 minutes and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analysed using a UV spectrometer at a wavelength of 267 nm.

7.4.8 Drug content[53]

This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a whatmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analysed using UV spectrometer.

7.4.9Assay

This test was performed by dissolving a 4 cm area of thin film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Whatmann filter

paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrophotometer.

7.4.10 Stability studies[54]

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F3 formulation was sealed in Aluminium packing laminated with polyethylene. Samples were kept at 40 c and 75% RH for 3 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

7.4.10 SEM analysis[56]

The morphological study of oral strip was done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the films. It also helps in determination of the distribution of API.

Results and Discussions

8 RESULTS AND DISCUSSION

8.1 PREFORMULATION STUDIES

8.1.1 Solubility

Solubility is expressed in terms of parts per million of solvent in which 1g of solid is soluble. Solubility of the powder in different solvents like water, ethanol etc was determined at 20°c.

8.2.2 Heavy metal content

The part of Lead per million parts of powder was examined by comparing sample solution with 10 ppm lead standard solution for 2 gm material.

8.2.3 Melting point

The melting point was carried out by using capillary tube method.

Table no 9: API characterization - Sitagliptin phosphate

S.No	Test	Specification	Result
1	Description	White powder	White powder
2	Solubility	Soluble in water	Complies
3	Taste	Bitter	Complies
4	Odor	Odorless	Complies
5	Heavy metals (ppm)	Should not be more than 20 ppm	Less
6	Melting point	Range :205-207° c	206 °c

8.2 CALIBRATION CURVE OF SITAGLIPTIN PHOSPHATE

Stock solution was prepared by 50 mg of Sitagliptin phosphate in 100 ml of water. From this stock solution 10 ml was withdrawn and diluted upto 100 ml using water. Calibration curve was prepared by using different concentration (20 µg/ml-100 µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 267 nm. The absorbance of various concentration measured at 267 nm is as follows in table 10. Standard curve of Sitagliptin phosphate is shown in figure 11.

Table no 10: Standard graph of Sitagliptin phosphate

S. No	Concentration µg/ml	Absorbance (267 nm)
1	20	0.228
2	40	0.436
3	60	0.641
4	80	0.864
5	100	0.998

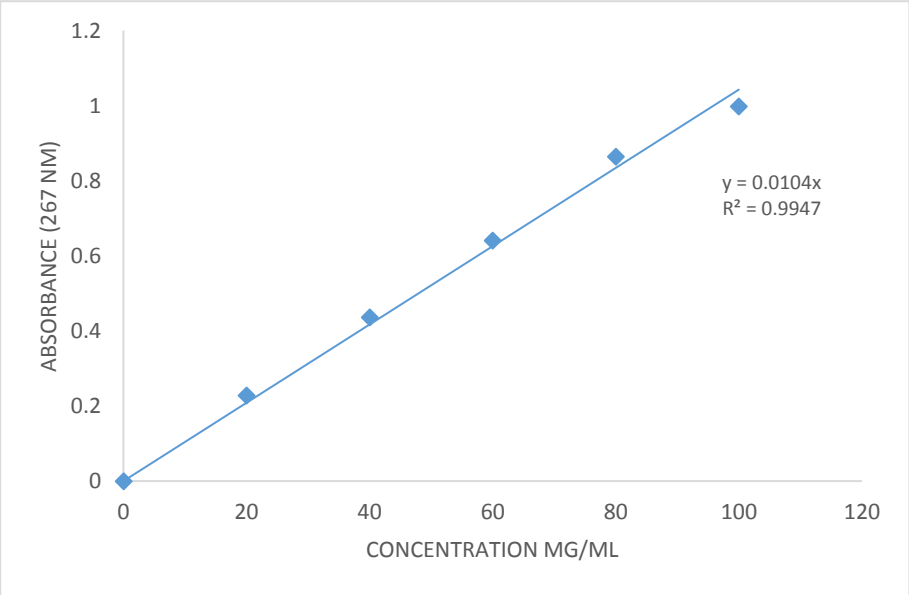

Fig 12: Standard graph of sitagliptin phosphate

8.3 FT-IR Studies

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of sitagliptin phosphate was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. Then the spectrum of dried mixture of drug and Pottasium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

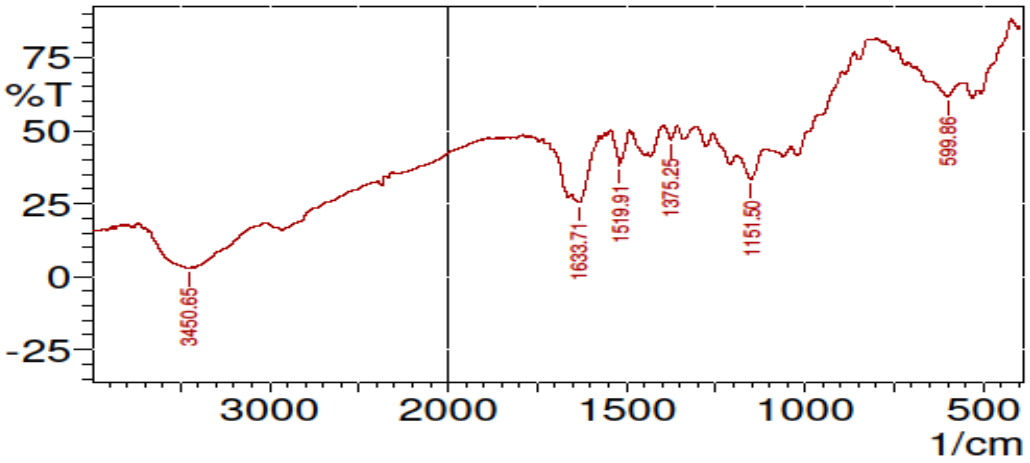

Fig 13: IR Spectra of Sitagliptin phosphate

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	599.86	61.564	5.035	644.22	561.29	15.901	1.269
2	1151.5	33.276	9.285	1190.08	1109.07	33.648	3.623
3	1375.25	46.849	4.9	1394.53	1357.89	11.258	0.773
4	1519.91	38.144	12.121	1543.05	1490.97	18.539	2.975
5	1633.71	25.357	7.832	1653	1575.84	36.913	3.504
6	3450.65	2.846	0.383	3473.8	3433.29	61.349	0.947

Table 11: IR Spectra of Sitagliptin phosphate

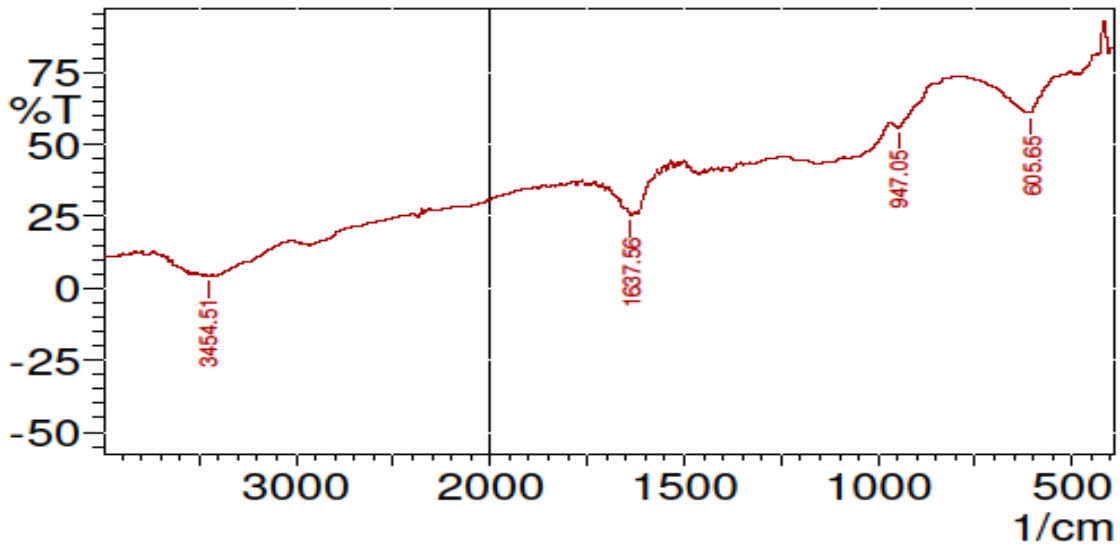

Fig 14: IR Spectra of HPMC E15

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	605.65	60.909	1.441	611.43	543.93	11.593	-0.046
2	947.05	55.948	4.051	966.34	860.25	22.036	1.415
3	1637.56	25.336	0.552	1651.07	1635.64	8.863	0.019
4	3454.51	4.455	0.023	3462.22	3452.58	13.003	0.013

Table 12: IR Spectra of HPMC E15

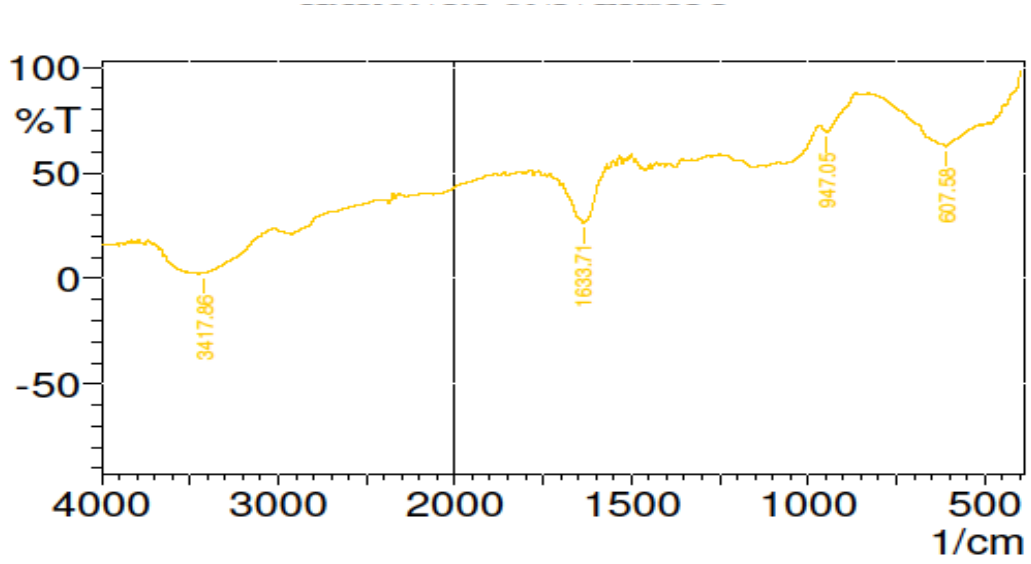

Fig 15: IR Spectra of HPMC E50

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	607.58	62.6036	1.6909	617.22	580.57	7.0633	0.1823
2	947.05	69.2787	6.4461	968.27	864.11	11.9589	1.7804
3	1633.71	26.4988	0.5196	1635.64	1627.92	4.3949	0.052
4	3417.86	2.4373	0.4349	3431.36	3394.72	57.4735	1.3563

Table 13 : IR Spectra of HPMC E50

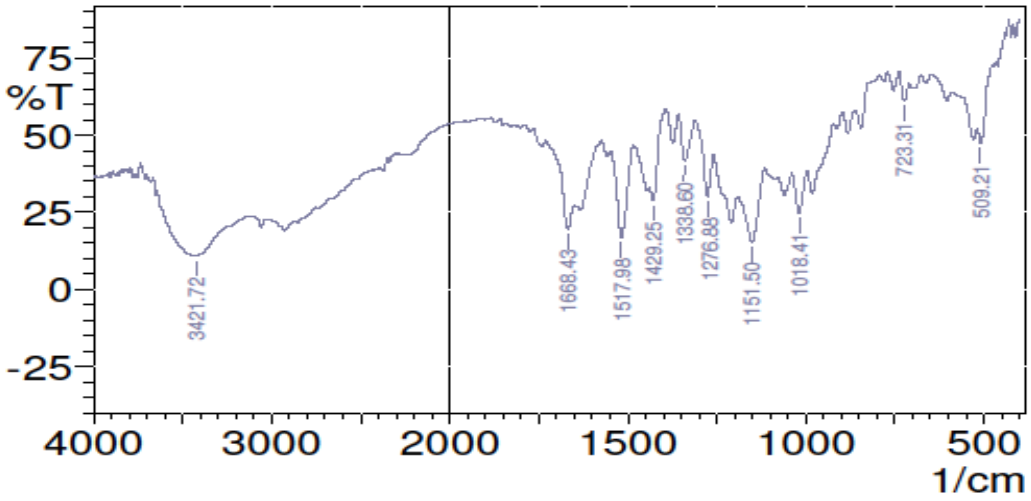

Fig 16: IR Spectra of Sitagliptin Phosphate + HPMC E15

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	509.21	47.35	9.618	518.85	478.35	9.733	1.195
2	723.31	61.02	7.496	738.74	711.73	5.127	0.733
3	1018.41	24.65	13.381	1037.7	997.2	20.677	3.675
4	1151.5	15.266	19.575	1192.01	1114.86	47.294	11.445
5	1276.88	30.095	17.342	1311.59	1259.52	19.707	3.575
6	1338.6	41.608	14.362	1357.89	1311.59	14.661	2.943
7	1429.25	28.691	9.694	1438.9	1392.61	17.337	0.844
8	1517.98	16.845	28.864	1546.91	1487.12	31.57	11.253
9	1668.43	19.401	13.906	1697.36	1649.14	27.051	4.454
10	3421.72	10.728	0.854	3433.29	3143.97	222.048	-7.282

Table 14: IR Spectra of Sitagliptin Phosphate + HPMC E15

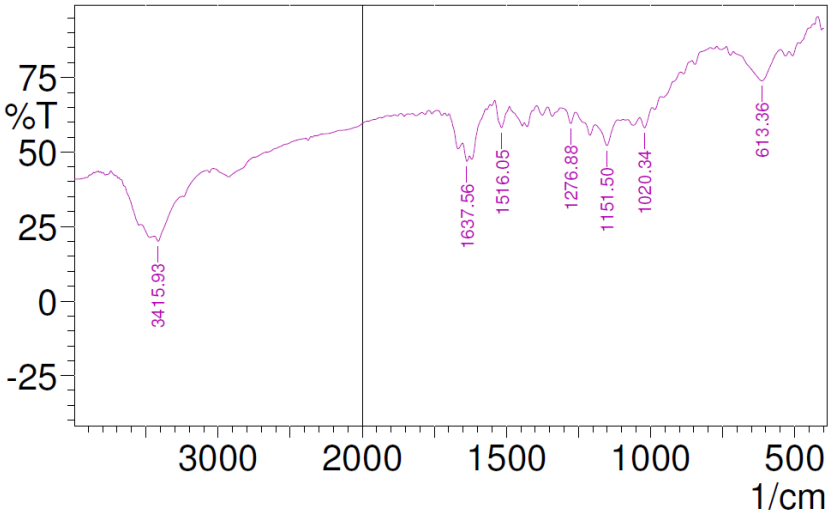

Fig 17: IR Spectra of Sitagliptin Phosphate + HPMC E50

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	613.36	73.909	10.211	713.66	549.71	16.616	4.239
2	723.31	58.154	4.755	1037.7	993.34	9.521	0.696
3	1151.5	52.214	7.835	1192.01	1112.93	19.454	1.923
4	1276.88	59.615	4.263	1311.59	1259.52	10.545	0.494
5	1516.05	58.215	8.182	1541.12	1489.05	10.788	1.51
6	1637.56	46.897	3.47	1653	1627.92	7.72	0.349
7	3415.93	20.069	3.568	3442.94	3248.13	109.507	0.838

Table 15: IR Spectra of Sitagliptin Phosphate + HPMC E50

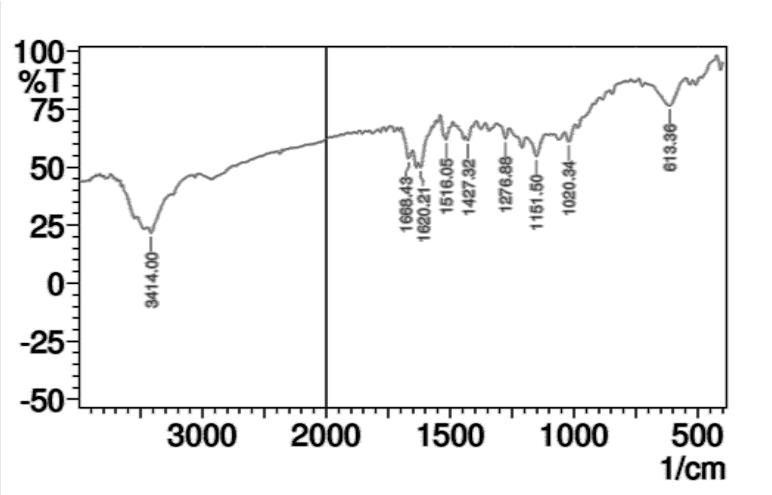

Fig 18: IR Spectra of sitagliptin Phosphate + HPMC E15 + HPMC E 50

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	613.36	76.445	10.358	680.87	549.71	11.719	3.618
2	1020.34	60.974	5.393	1037.7	995.27	8.238	0.762
3	1151.5	54.71	8.866	1192.01	1114.86	17.204	2.007
4	1276.88	62.386	4.943	1311.59	1261.45	9.048	0.564
5	1427.32	61.595	3.497	1438.9	1411.89	5.287	0.302
6	1516.05	61.92	7.385	1539.2	1500.62	7.169	1.133
7	1620.21	50.03	4.028	1627.92	1571.99	12.983	0.281
8	1668.43	53.824	6.898	1699.29	1651.07	11.082	1.039
9	3414	21.642	4.53	3442.94	3250.05	101.18	1.264

Table 16: IR Spectra of sitagliptin Phosphate + HPMC E15 + HPMC E 50

8.4 EVALUATION PARAMETERS

8.4.1 Thickness

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5 %. The thickness of fast dissolving films of all formulations given in table 17 and figure 19.

8.4.2 Folding endurance

To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between100-150. The folding endurance of fast dissolving films of all formulations given in table 17 and figure 19.

8.4.3 Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula.

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

The tensile strength of fast dissolving films of all formulations given in table 17 and figure 19.

8.4.4 Percentage elongation

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

The percentage elongation of fast dissolving films of all formulations given in table 17 and figure 19.

8.4.5 *In-vitro* disintegration

Petri dish method

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely.

The in-vitro disintegration time of fast dissolving films of all formulations given in table 17 and figure 19.

Table 17: Evaluation parameters

Formulations	Thickness (mm)	Folding endurance	Tensile strength (g/cm^2)	% elongation	*In-vitro* disintegration time(sec)
F1	0.58	9	48.41	8	25
F2	0.55	10	51.18	9	28
F3	0.59	13	62.04	11	20
F4	0.51	9	54.25	9	31
F5	0.53	11	53.68	10	35
F6	0.52	11	52.33	8	27
F7	0.55	12	56.45	7	36
F8	0.57	1.0	57.62	9	32
F9	0.53	9	48.63	10	35

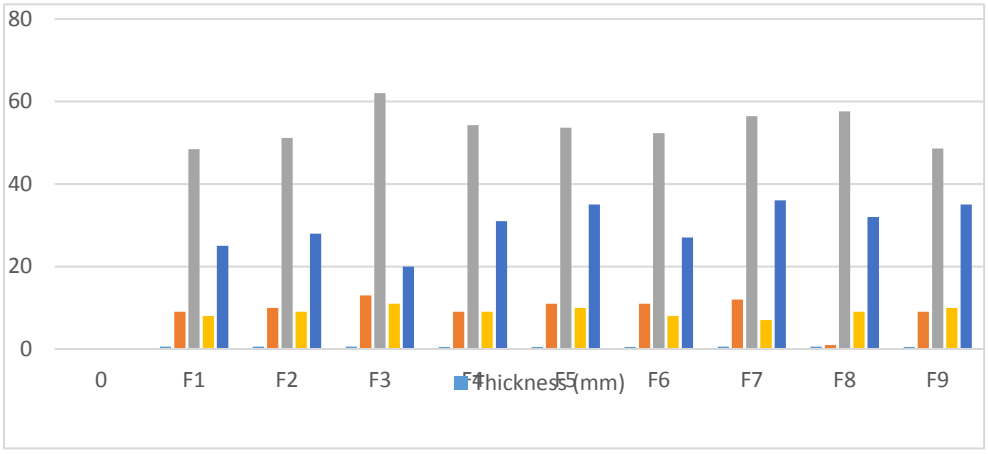

Fig 19: Bar chart of evaluation parameters

8.5 WEIGHT VARIATION

8.5.1 Weight variation

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation. The weight variation of fast dissolving films of all formulations given in table 18 and figure 20.

Table no 18: Weight Variation

Formulations	Weight variation (mg)
F1	69
F2	68
F3	68.2
F4	69.4
F5	70.2
F6	69.4
F7	68.3
F8	70.6
F9	69.2

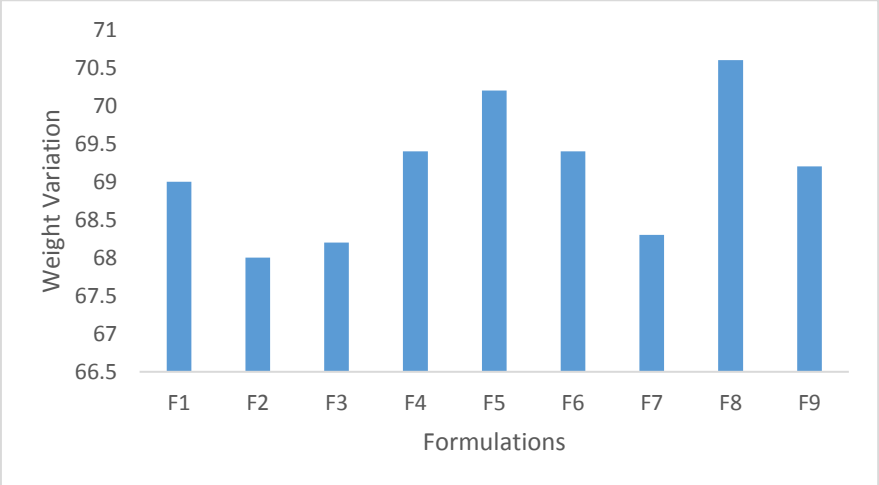

Fig 20: Bar chart of weight variation

8.6 DRUG CONTENT AND ASSAY

8.6.1 Drug content

This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a whatmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analysed using UV spectrometer. The drug content result of all the formulations shown in table 19 and the values depicted as graphical representation in figure 21.

8.6.2 ASSAY

This test was performed by dissolving a 4 cm area of thin film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Whatmann filter

paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrophotometer. The assay result of all the formulations shown in table 19 and the values depicted as graphical representation in figure 21.

Table no 19: Drug content and Assay

Formulations	Drug content (mg)	Assay (%)
F1	24.86	97.25
F2	23.25	98.14
F3	25.01	99.87
F4	22.91	98.34
F5	24.55	98.45
F6	23.88	97.22
F7	24.78	98.33
F8	24.63	97.87
F9	23.52	98.12

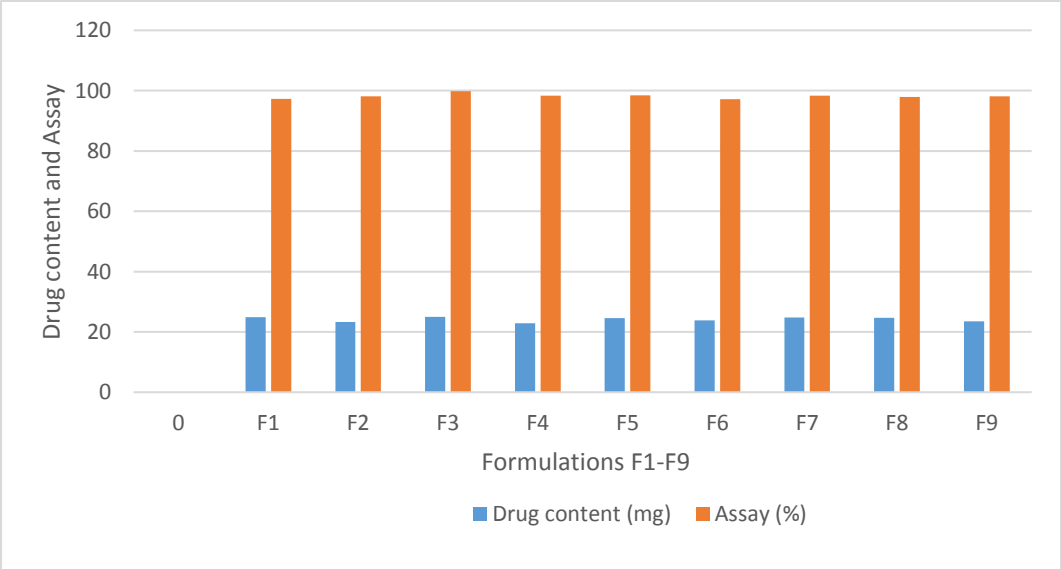

Fig 21: Bar chart of drug content and assay

8.7 IN-VITRO DISSOLUTION

***In-vitro* dissolution**

900 ml of o.1 N HCL was used as a media, at was maintained at 37 +0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. 5 ml of the sample were taken every 2 minutes and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 267 nm. In-vitro dissolution profile data of all formulations given the table 20-28 and figure 22-30. The Percentage Cumulative Drug Release of F1 - F9 shown in table 29 Figure 31. The in-vitro dissolution profile data of marketed formulation depicted in table 30 and figure 32. The comparison of in-vitro release data of marketed formulation and formulation 3 shown in table 31 and figure 33.

Table 20: In-vitro dissolution of F1

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.043	4.134	18.60	18.6	19
1.0	0.073	7.019	31.58	31.6	32
1.5	0.121	11.63	52.35	52.4	52
2.0	0.164	15.76	70.96	71.0	71
2.5	0.193	18.65	83.94	84.0	84
3.0	0.214	20.57	92.59	93.0	93

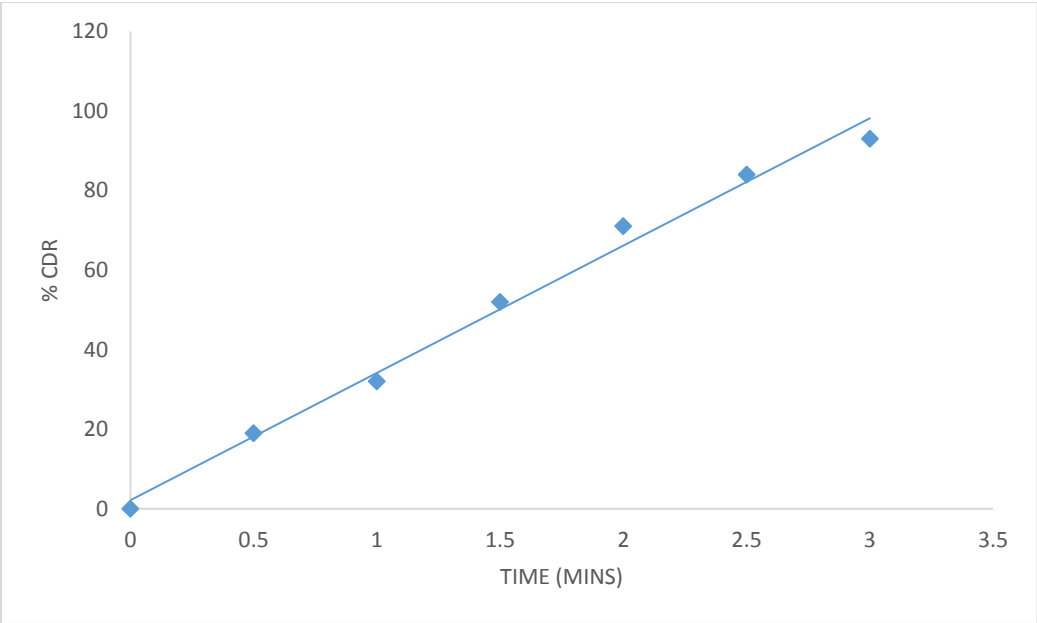

Fig 22: In-vitro dissolution of F1

Table 21: In-vitro dissolution of F2

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.049	4.71	21.20	21.2	21
1.0	0.083	7.98	35.91	36.0	36
1.5	0.135	12.98	58.41	58.4	58
2.0	0.156	15.1	67.5	68.0	68
2.5	0.198	19.03	85.67	86.0	86
3.0	0.225	21.63	97.36	97.3	97

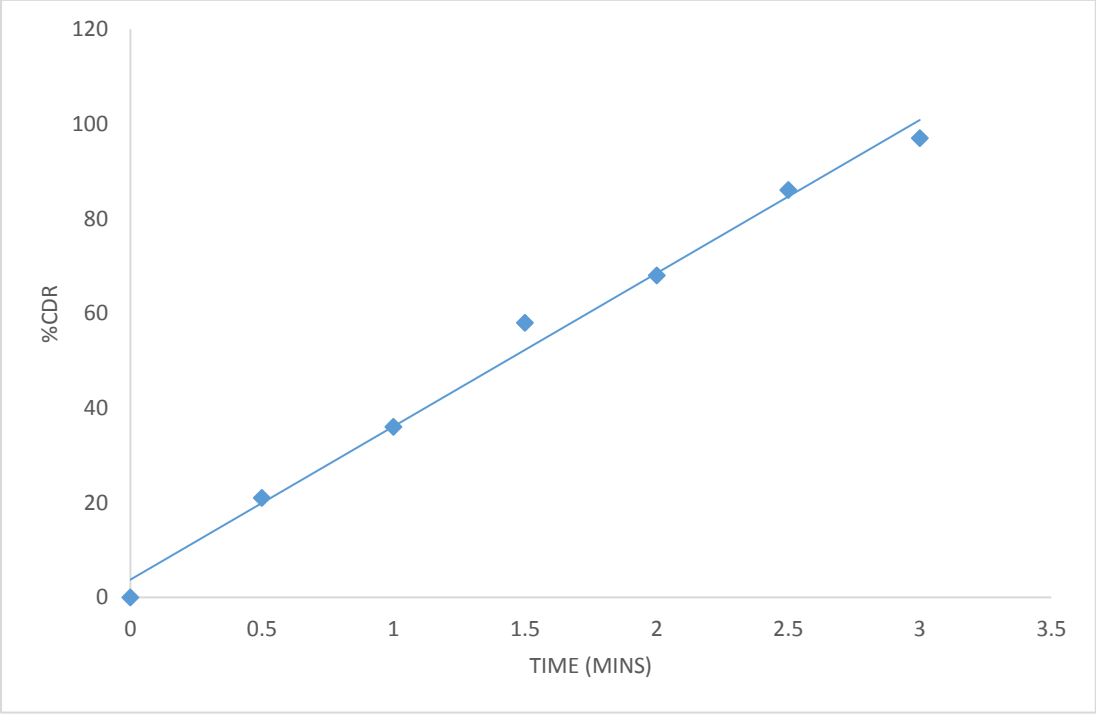

Fig 23: In-vitro dissolution of F2

Table 22: In-vitro dissolution of F3

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.050	4.807	17.30	17.3	17
1.0	0.086	8.260	37.21	37.2	37
1.5	0.100	9.611	43.26	43.3	43
2.0	0.181	17.40	78.31	78.3	78
2.5	0.220	21.15	82.21	82.2	82
3.0	0.228	23.36	98.63	98.6	99

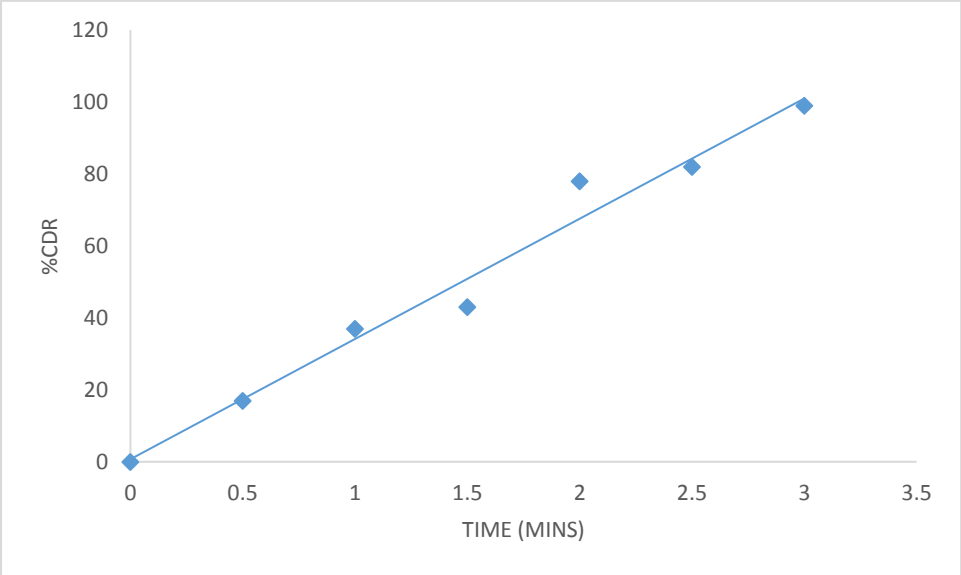

Fig 24: In-vitro dissolution of F3

Table 23: In-vitro dissolution of F4

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.052	5.01	22.54	23.0	23
1.0	0.098	9.42	42.40	42.4	42
1.5	0.134	12.88	58.10	58.1	58
2.0	0.169	16.25	73.13	73.1	73
2.5	0.188	18.07	81.35	81.3	81
3.0	0.220	21.15	95.20	95.2	95

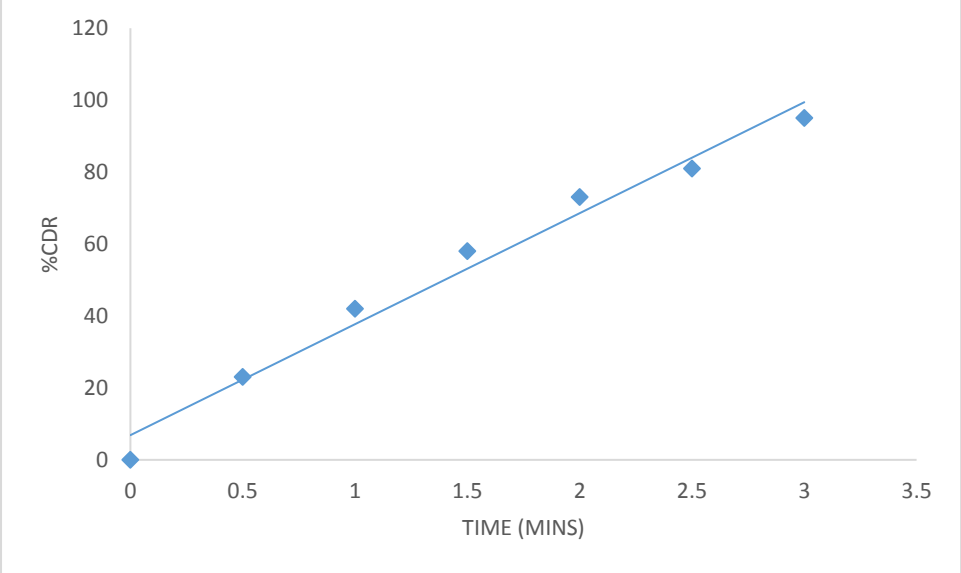

Fig 25: In-vitro dissolution of F4

Table 24: In-vitro dissolution of F5

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.053	5.09	22.93	23.0	23
1.0	0.095	9.13	41.10	41.1	41
1.5	0.124	11.9	53.65	54.0	54
2.0	0.166	15.9	71.82	72.0	72
2.5	0.182	17.5	78.85	79.0	79
3.0	0.218	20.9	94.32	94.3	94

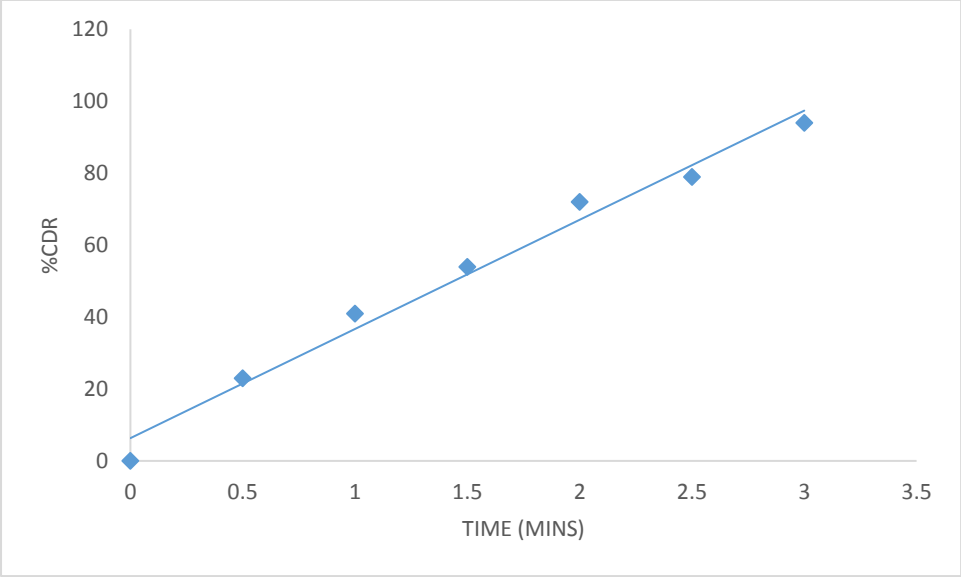

Fig 26: In-vitro dissolution of F5

Table 25: In-vitro dissolution of F6

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.049	4.71	21.20	21.2	21
1.0	0.088	8.46	38.08	38.0	38
1.5	0.132	12.7	57.16	57.2	57
2.0	0.059	15.3	68.8	69.0	69
2.5	0.194	18.7	83.9	84.0	84
3.0	0.213	20.5	92.16	92.2	92

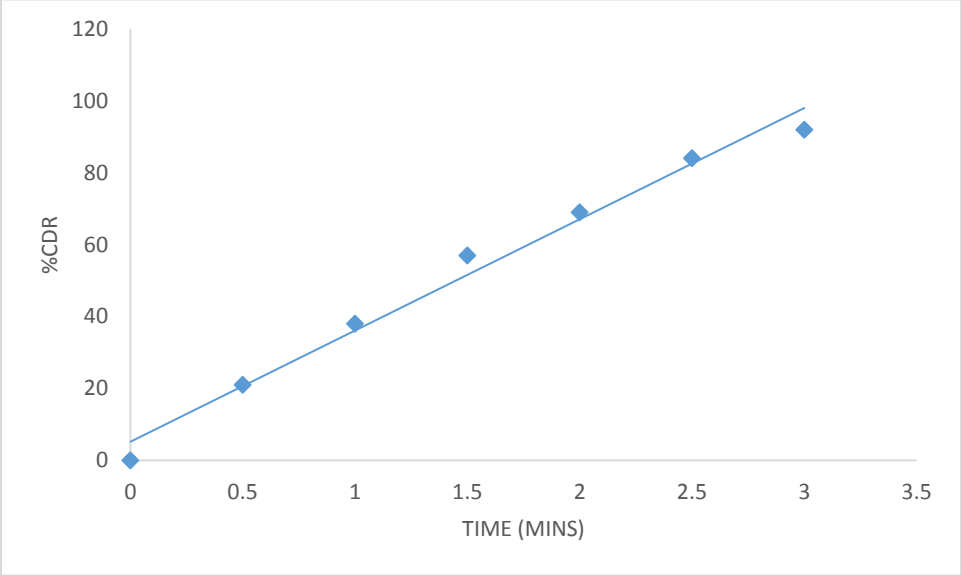

Fig 27: In-vitro dissolution of F6

Table 26: In-vitro dissolution of F7

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.048	4.62	20.76	20.8	21
1.0	0.088	8.46	38.07	38.1	38
1.5	0.128	12.31	55.39	55.4	55
2.0	0.159	15.29	68.80	69.0	69
2.5	0.189	18.17	81.77	82.0	82
3.0	0.223	21.44	96.49	96.5	97

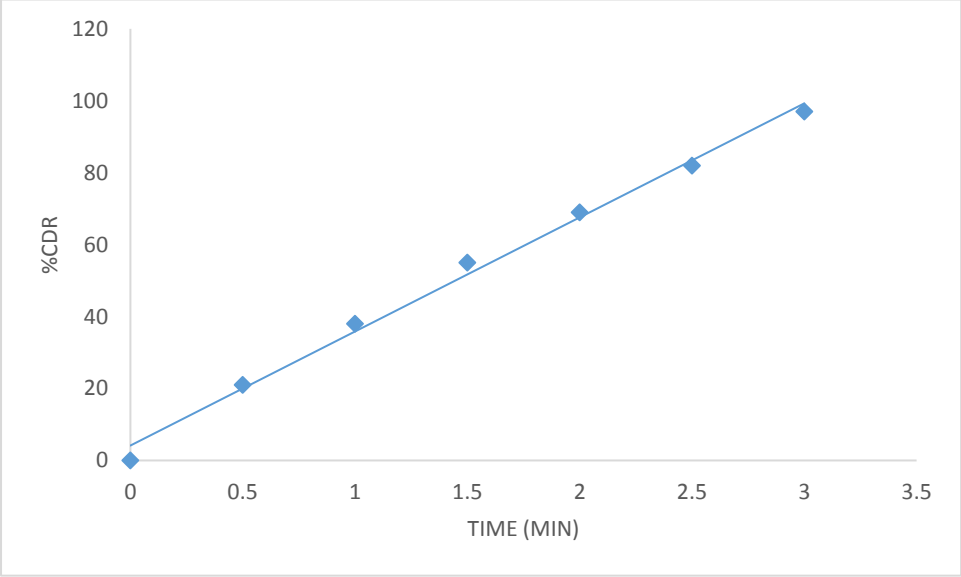

Fig 28: In-vitro dissolution of F7

Table 27: In-vitro dissolution of F8

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.039	3.75	16.88	16.9	17
1.0	0.078	7.52	33.75	33.8	34
1.5	0.134	12.88	57.98	58.0	58
2.0	0.164	15.76	70.96	71.0	71
2.5	0.190	18.27	82.21	82.2	82
3.0	0.224	21.54	96.92	97.0	97

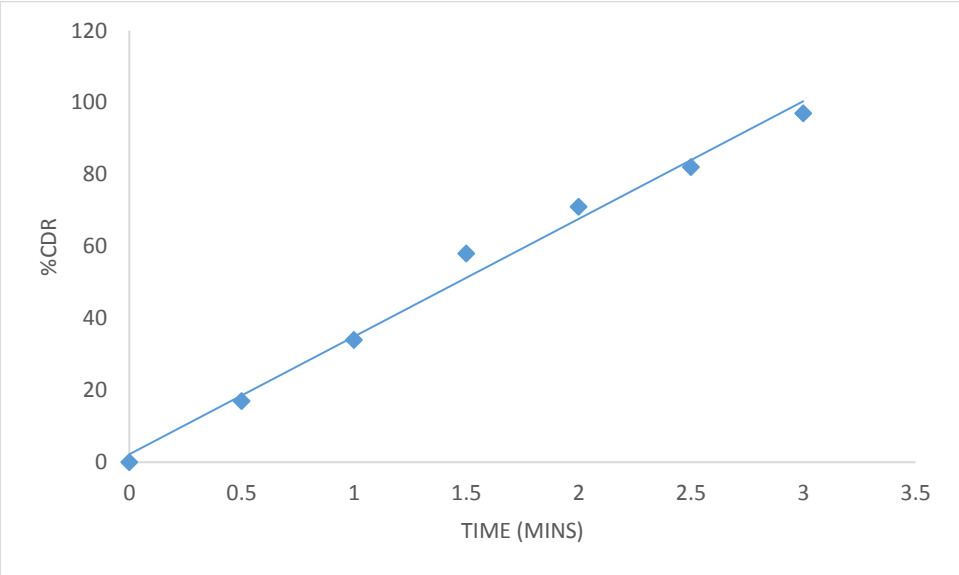

Fig 29: In-vitro dissolution of F8

Table 28: In-vitro dissolution of F9

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.046	4.42	19.90	19.9	20
1.0	0.082	7.88	35.48	35.5	36
1.5	0.140	13.46	60.58	60.6	61
2.0	0.162	15.58	70.1	70.1	70
2.5	0.186	17.88	80.5	81.0	81
3.0	0.221	21.25	95.6	96.0	96

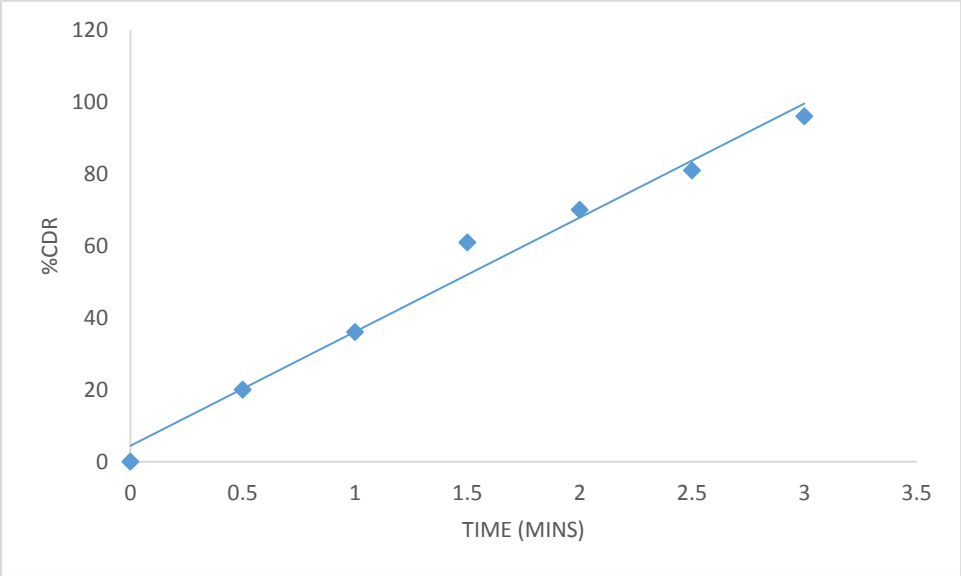

Fig 30: In-vitro dissolution of F9

Table no 29: *In-vitro* dissolution of F1-F9

Percentage drug released									
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.5	19	21	17	23	23	21	21	17	20
1.0	32	36	37	42	41	38	38	34	36
1.5	52	58	43	58	54	57	55	58	61
2.0	71	68	78	73	72	69	69	71	70
2.5	84	86	82	81	79	84	82	82	81
3.0	93	97	99	95	94	92	97	97	96

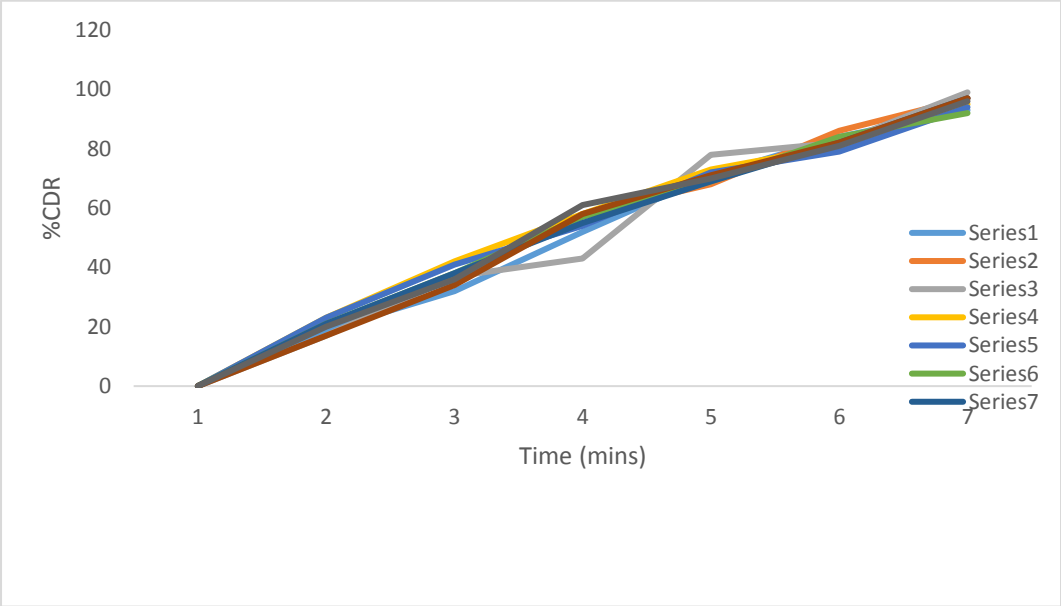

Fig 31: *In-vitro* dissolution of F1-F

8.8 In-vitro drug release profile data of marketed formulation

Table no 30: *in-vitro* drug release profile data of marketed formulation

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
10	0.038	3.65	16.44	16.4	16
20	0.079	7.59	34.2	34.2	34
30	0.110	10.58	47.6	48.0	48
40	0.147	14.13	63.61	64.0	64
50	0.178	17.16	77.02	77.0	77
60	0.218	20.46	94.33	94.3	94

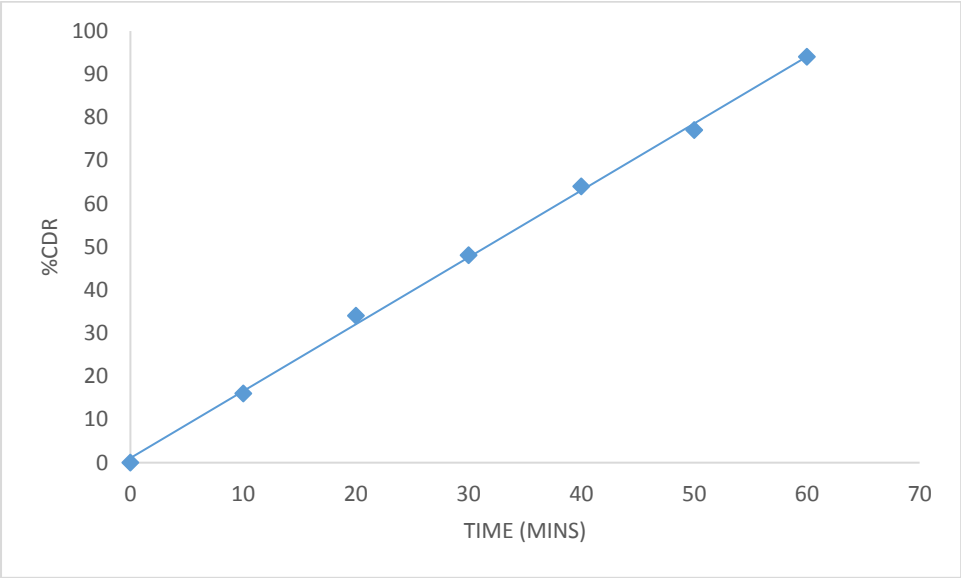

Fig 32: *in-vitro* drug release profile data of marketed formulation

8.9 Comparison of in-vitro drug release data of marketed formulation and formulation 3

Table no 31: Comparison of in-vitro drug release data of marketed formulation and formulation 3

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release	Cumulative percentage release of formulation 3
10	0.038	3.65	16.44	16.4	16	17
20	0.079	7.59	34.2	34.2	34	37
30	0.110	10.58	47.6	48.0	48	43
40	0.147	14.13	63.61	64.0	64	78
50	0.178	17.16	77.02	77.0	77	82
60	0.218	20.46	94.33	94.3	94	99

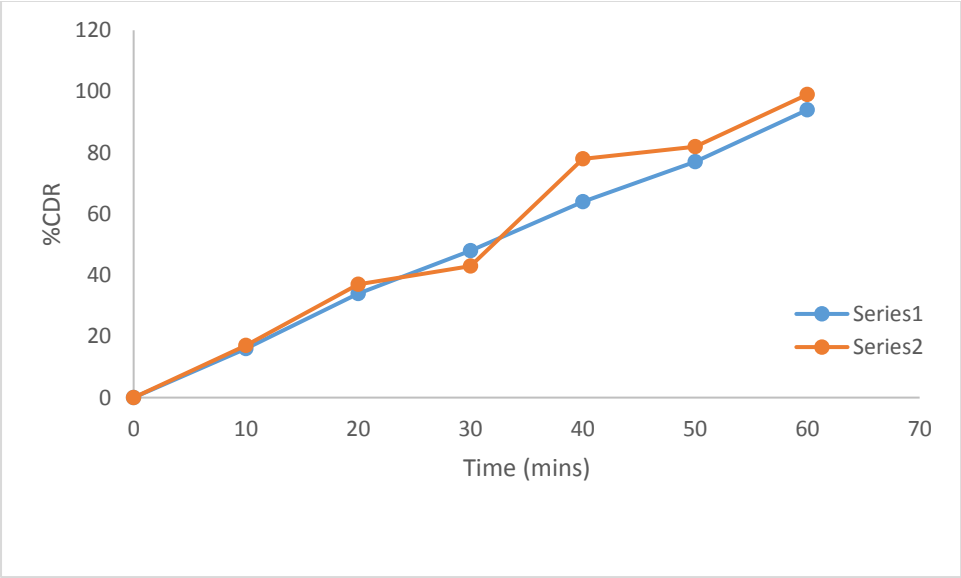

Fig 33: Comparison of in-vitro drug release data of marketed formulation

and formulation 3

8.10 STABILITY STUDIES (F3)

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F3 formulation was sealed in Aluminium packing laminated with polyethylene. Samples were kept at 40 c and 75% RH for 3 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

Table no 32: Stability studies [Condition (40°C/75%RH)]

Parameters	Initial	1 month	3 months
Thickness (mm)	0.59	0.59	0.59
Folding endurance	13	13	12
Tensile strength (gm/cm^2)	54.25	54.25	53.01
in-vitro disintegration time (sec)	20	20	22
in-vitro dissolution (%)	99.26	99.26	99.06

Test frequency: Initial & 3 months

- It is found to be all the physical and chemical parameters are satisfactory based on initial stability data.
- Photo stability studies have shown that the medicinal product is non-light sensitive.

8.11 SEM ANALYSIS

The morphological study of oral strip was done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the films. It also helps in determination of the distribution of API.

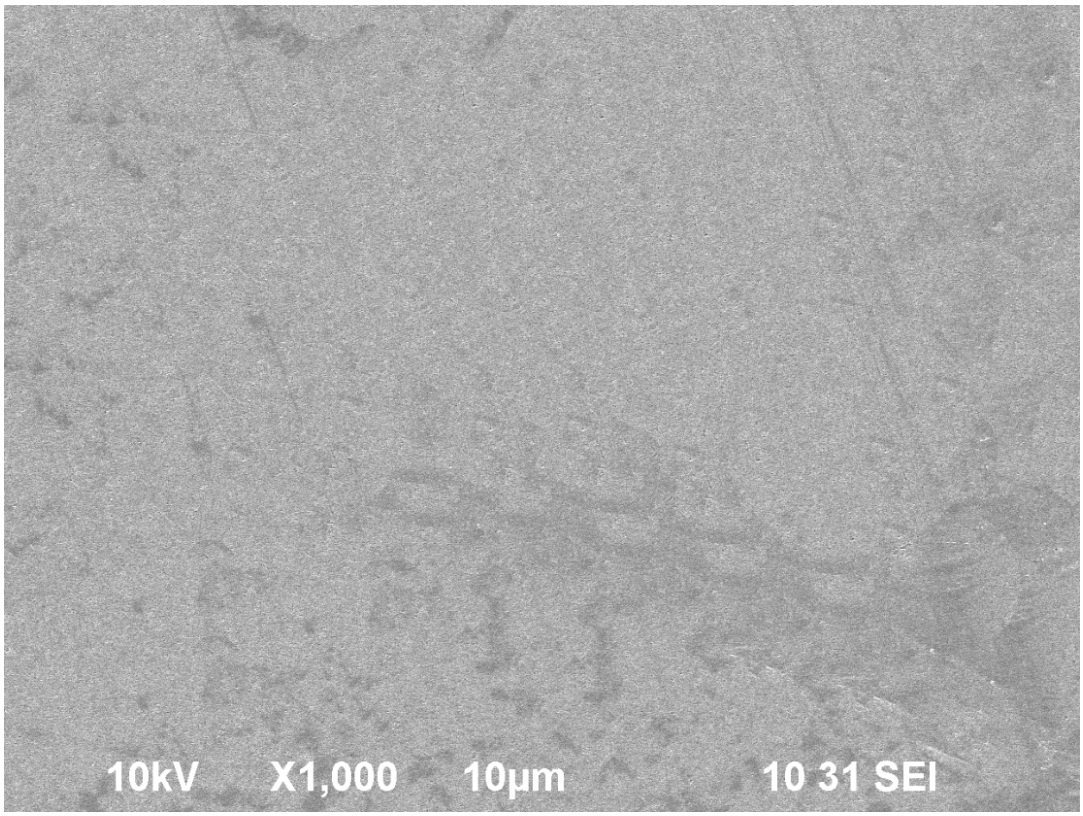

Fig 34 : SEM images

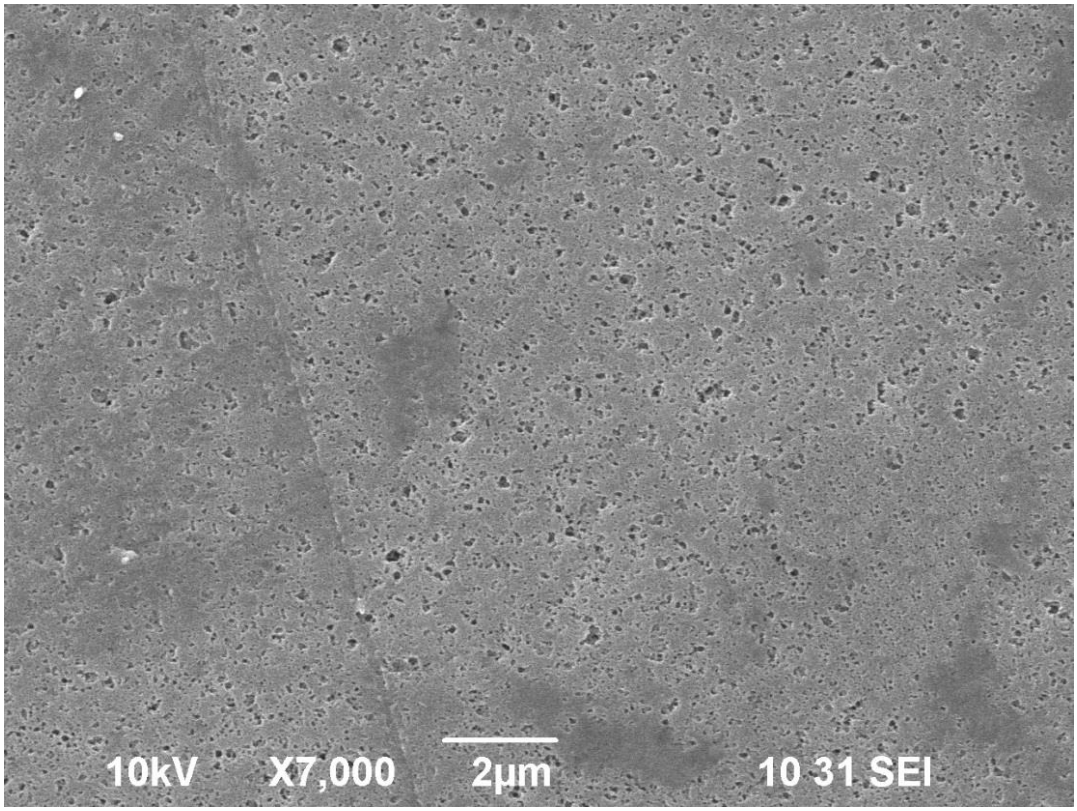

Fig 35: SEM images

8.12 DISCUSSION

The present investigation was undertaken to formulate Sitagliptin phosphate oral films. For the treatment of Diabetes mellitus.

F1-F3 were carried out with HPMC E15 cps, PEG 400, sodium saccharin, citric acid and flavor. The films were clear and transparent. The thickness also uniform. The flexibility also good. The films shown good mechanical properties. According to the assay result the drug was properly loaded in the film.

F4-F6 were carried out with HPMC E50, propylene glycol, sodium saccharin, citric acid and flavor. The films shows good appearance. The thickness also not uniform. The flexibility of the film was not good. The percentage drug release was found to be.

F7 was formulated with HPMC E15, propylene glycol, sodium saccharin, citric acid and flavor. The appearance of the film was also good but the thickness and disintegration time was more.

F8 was formulated with HPMC E50, PEG 400, sodium saccharin, citric acid and flavor.

F9 was formulated with HPMC E15 & E50 without the addition of plasticizers. The formulated films were more brittleness.

Among all the formulations F3 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible.

The morphological study (SEM) of F3 shows more porous. Therefore rapid drug release was achieved for the immediate onset of action.

The stability studies were performed for about 1 month and 3 months. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release.

The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore the oral films have considerable advantage over the conventional dosage forms.

Summary and Conclusion

9. SUMMARY AND CONCLUSION

The primary objective of this work was to develop a mouth dissolving film with Sitagliptin phosphate, along with basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor.

The films were prepared by solvent casting method.

HPMC E50 cps, which was not able to impart thickness to the film. HPMC E15 shown good flexibility.

The plasticizer propylene glycol which was not able to impart flexibility and folding endurance to the film. PEG 400 produced good folding endurance, tensile strength and percent elongation.

The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties.

The F3, shown less disintegration time of 20 seconds and 99% drug released within 3 minutes while the marketed formulation took 1 hour.

Therefore rapid drug release was achieved for immediate onset of action which is beneficial when compared to conventional tablet dosage form.

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